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VOLUME 58
1947

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO, ILL.

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Archives of Neurology and Psychiatry

VOLUME 58

JULY 1947

NUMBER 1

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RATE OF REGENERATION OF SENSORY NERVE FIBERS

SYDNEY SUNDERLAND, M.D., D.Sc.
MELBOURNE, AUSTRALIA

THIS paper is concerned with the rate of regeneration of sensory fibers, calculated on the basis of the rate of advance of Tinel's sign, during the recovery of injured peripheral nerves. Though it is generally accepted that the eliciting of Tinel's sign is evidence of the presence of "young axis-cylinders in the process of regeneration," there has been no histologic confirmation of the structure of the fiber at the site of percussion. The present account is not concerned either with the morphologic features of the recovering nerve fiber or with the prognostic significance of the sign, but is confined to a consideration of the rate at which it advances.

With the exception of Seddon, Medawar and Smith,¹ those who have devoted attention to the estimation of rates of recovery on this basis have omitted to indicate whether, in any instance, this was obtained by a single calculation or from data provided by successive examinations spread over the process of recovery; furthermore, they give the impression that in any individual case the rate is constant throughout the process of repair. An advancing Tinel's sign, however, presents an opportunity of studying the rate of growth of sensory fibers, in any individual case, over different segments of the nerve and at various periods after injury and suture; thus, it should be possible to ascertain whether the rate is constant or whether it diminishes progressively. For calculation of the rate by successive examinations, it is not necessary to know the duration of the initial delay, i. e., the delay occurring at the site of the lesion before the axons begin to grow down the distal segment. This is an advantage, since there is no method of accurately estimating this period in any individual case except when Tinel's sign can be recognized immediately below the lesion.

The observations of Seddon, Medawar and Smith¹ were made on 6 sutured nerves provided by 4 patients. They appear to have

From the Department of Anatomy and Histology, University of Melbourne.

1. Seddon, H. J.; Medawar, P. B., and Smith, H.: Rate of Regeneration of Peripheral Nerves in Man, *J. Physiol.* 102:191-215 (Sept. 30) 1943.

been convinced, however, that the rate was constant and, on the graph obtained by plotting time against distance, constructed a straight growth line representing a constant rate in spite of two indications to the contrary:

1. The latent period, obtained by extrapolation, had a negative value in 5 of the cases.

2. A curve would have suited their findings in some cases just as satisfactorily, particularly if certain discrepant readings had been discarded. For example, in their figure 8, retrogression, rather than advance, of Tinel's sign is shown by the fourth and fifth readings for the ulnar nerve and by the fifth and sixth readings for the median nerve. In these cases an analysis of the data strongly suggests a progressively diminishing rate.

MATERIAL

Eleven patients provided 12 peripheral nerve injuries on which the observations here reported were based. In 3 cases the lesion was of the type defined as axonotmesis; in the remaining 9 cases the nerve had been sutured. The distances and times in each case were accurately measured. The sign was elicited by gentle and localized percussion, and, so far as was possible, precautions were taken to avoid transmission of the force to segments of the nerve proximal to the site of percussion. The number of observations on each nerve was not constant, since the sign was not elicited at every examination; thus it was not possible in every case to determine whether the rate was a constant or a diminishing one.

It is not claimed that final conclusions can be drawn from such a small series of cases. It is hoped that other workers in this field will make similar contributions, so that a series of cases sufficiently large and detailed for statistical analysis can be gathered from a number of sources. It is regrettable that this sign has been studied in detail by few who have investigated the regeneration of nerves. In almost every instance there has been no more than a brief reference to Tinel's sign, when so much could have been learned from precise measurements of time and distance made at successive examinations throughout the period of recovery.

OBSERVATIONS

Full details relating to the progress of Tinel's sign and the calculated rate of regeneration in each nerve are given in the table, and only brief case reports are given here.

CASE 24.—W. J. A. sustained a gunshot wound of the left ulnar nerve in the medial epicondylar groove on July 1, 1941. There was complete interruption of conduction in the nerve, which, however, was intact when seen in the wound. The nerve recovered spontaneously.

CASE 94.—M. G. sustained a perforating gunshot wound of the right thigh on Oct. 26, 1942, which resulted in complete interruption of conduction in the sciatic nerve. Spontaneous recovery occurred in the medial popliteal division but

Details Relating to Advance of Tinel's Sign and Rate of Regeneration Calculated Therefrom

Nerve; Nature of Nerve Injury	Case No.	Date of Injury	Date of Suture	Date of Examination *	Time, Days	Level of Tinel's Sign Below Lesion, Mm.	Distance Traveled by Axons, Mm.	Rate of Regen- eration, Mm. per Day
Median Suture	322	10/21/44	2/21/45	9/27/45 (218)	54	180	90	1.7
				11/20/45 (272)	114	270	85	0.7
				3/14/46 (386)	19	355	15	0.8
				4/ 2/46 (405)	100	370	60	0.6
				7/11/46 (505)		430		
Ulnar Lesion in continuity	24	7/ 1/41	8/ 9/41 (39)	111	100	170	1.5
				11/28/41 (150)		270		
Suture	105	12/22/42	12/24/42	3/ 5/43 (71)	41	150	100	2.4
				4/15/43 (112)		250		
				5/18/43 (105)	63	190	80	1.3
	127	12/ 8/42	2/ 2/43	7/23/43 (168)	63	270		
	182	5/17/41	9/24/43	11/ 9/43 (46)	63	130	120	1.9
				1/11/44 (109)		250		
	230	4/ 3/44	4/ 4/44	5/ 7/44 (33)	38	15	95	2.5
				6/14/44 (71)	92	110	180	2.0
				9/14/44 (163)	36	290	30	0.8
	322	10/21/44	6/ 6/45	10/20/44 (199)		320		
				9/27/45 (113)	54	200	85	1.6
				11/20/45 (167)	114	285	70	0.6
Sciatic Lesion in continuity	270	6/30/43	3/14/46 (281)	19	355	15	0.8
				4/ 2/46 (300)	100	370	50	0.5
				7/11/46 (400)		420		
	270	6/30/43	3/15/44 (258)	124	100†	200	1.6
				7/17/44 (382)	116	300†	40	0.3
				11/10/44 (498)		340†		
	94	10/26/42	2/ 5/45	5/24/45 (108)	98	280	160	1.6
				8/30/45 (206)	42	440	50	1.2
				10/11/45 (248)	42	490	30	0.7
	122	12/28/42	9/ 4/43	11/22/45 (290)	222	520	110	0.5
				7/ 2/46 (512)		630		
				1/11/44 (129)	121	280	260	2.1
	137	10/31/42	7/19/44	5/11/44 (250)	70	540	100	1.4
				7/23/44 (320)		640		
				12/ 6/44 (140)	166	300	270	1.6
Lateral popliteal Lesion in continuity	174	4/ 7/43	5/21/45 (306)		570		
				3/ 9/44 (337)	98	150	70	0.7
				6/15/44 (435)		220		

* The figure in parentheses after each date is the number of days between the time of suture (or injury in cases of axonotmesis) and the time of the examination.

† Measurements taken from the head of the fibula.

was so little advanced in the lateral popliteal division that the nerve was explored on Feb. 5, 1945. The partially severed lateral division was repaired. The progress of Tinel's sign, measured from the level of the suture, and the rates calculated refer to the lateral popliteal division of the nerve.

CASE 105.—K. T. F. lacerated his right elbow on a piece of glass on Dec. 22, 1942. The ulnar nerve had been divided at a point 5 cm. below the medial epicondyle of the humerus and was sutured two days later.

CASE 122.—P. H., on Dec. 28, 1942, sustained a perforating gunshot wound of the left buttock, with a comminuted fracture of the acetabulum and the head and neck of the femur. The sciatic nerve, which was completely severed, was not sutured until Sept. 4, 1943.

CASE 127.—D. F. W. sustained a laceration of the right elbow on Dec. 8, 1942, which resulted in complete interruption of conduction in the ulnar nerve. At exploration, on Feb. 2, 1943, the nerve was observed to be severed in the medial epicondylar groove. It was sutured.

CASE 137.—C. G. W. sustained a penetrating gunshot wound of the left thigh on Oct. 31, 1942, which resulted in a fracture of the middle third of the femur and severance of the sciatic nerve. The nerve was sutured on July 19, 1944.

CASE 174.—S. E. N. sustained a gunshot wound of the right knee in the region of the neck of the fibula on June 12, 1941. At an operation on the infected upper end of the fibula, on April 7, 1943, the lateral popliteal nerve was damaged and conduction completely interrupted. The nerve recovered spontaneously, but restoration of function was not complete.

CASE 182.—J. S., on May 17, 1941, sustained a gunshot wound of the right elbow with a fracture of the lower end of the humerus and complete interruption of conduction in the ulnar and median nerves. The patient was a prisoner of war, and I did not examine him until July 13, 1943, when the median nerve was recovering but interruption of conduction in the ulnar nerve was still complete. On Sept. 24, 1943 the ulnar nerve was explored, sutured just above the medial epicondyle of the humerus and transposed anterior to it. This case is of interest in view of the long period intervening between the injury and the suture of the nerve.

CASE 270.—J. L. W. sustained a perforating gunshot wound of the left buttock on June 30, 1943, which fractured the femur. There was complete interruption of conduction in the sciatic nerve, which was intact when seen in the wound. Spontaneous recovery in the medial popliteal division was satisfactory; the only recovery recorded for the lateral division was an advancing Tinel sign.

CASE 290.—A. B. R. was involved in an automobile accident on April 3, 1944, in which he sustained a laceration of the right elbow. The ulnar nerve was severed in the medial epicondylar groove of the humerus and was sutured the day after the injury.

CASE 322.—O. A. R. sustained a gunshot wound of the upper third of the left arm on Oct. 21, 1944, which completely severed the ulnar and median nerves and the brachial artery.

On Feb. 21, 1945, the median nerve was sutured under moderate tension and the ulnar nerve under such considerable tension that it was thought advisable to reexplore and resuture it on June 6, 1945, at which time the union was effected without tension.

This is an interesting case in that the nerves were damaged at about the same level. After suture, Tinel's sign had advanced 200 mm. in one hundred and thirteen days in the ulnar nerve and 180 mm. in two hundred and eighteen days in the median nerve. The difference in the distances covered is not necessarily due to a faster rate of growth of the ulnar axons; it could be attributed to the more accurate operative apposition of the stumps of the ulnar nerve, resulting in a shorter delay at the site of suture before the entry of axons into the distal segment. That the latter is the more likely explanation is supported by the observation that farther distally the calculated rates for the two nerves approximated each other.

CONCLUSIONS

In analyzing the results, it should be borne in mind that the value obtained for the rate of regeneration will depend on the length of the nerve over which it is measured. Over considerable lengths a gradual slowing of the regenerative processes would result in a reduced over-all calculation for the rate, while over very short lengths the calculated rate would be greater in the early stages. Frequent readings over short distances will give the most accurate results.

The reported observations demonstrate that after suture regenerating sensory fibers advance at a progressively diminishing rate. The following generalizations appear to be justified cases of suture in the proximal part of the limb.

1. In the early stages of recovery (up to one hundred and twenty days) the rate fell from 2.5 to 2 mm. per day. The distances over which the calculations were made varied from 95 to 120 mm.—it is probable that the early rate would have approximated 3 mm. per day had the calculations been based on more frequent readings at this stage.

2. In the intermediate stages of recovery (from one hundred and twenty to two hundred days) the rate was approximately 1.6 mm. per day.

3. Over the terminal stages of recovery (two hundred to five hundred days) the rate fell from 0.8 to 0.5 mm. per day. In this phase the rate was, in most instances, calculated over very short distances (15, 15, 30, 30, 40, 50, 60, 70, 70, 85 and 110 mm.).

The results are comparable with those previously obtained for regenerating motor fibers,² for which, it was believed, the method employed gave the rate of advance of functionally mature fibers. The question of functional maturity requires further definition, but the opinion was expressed by Gutmann, Guttmann, Medawar and Young³ and by

2. Sunderland, S.: Course and Rate of Regeneration of Motor Fibers Following Lesions of the Radial Nerve, *Arch. Neurol. & Psychiat.* **56**:133-157 (Aug.) 1946; Rate of Regeneration of Motor Fibers in the Ulnar and Sciatic Nerves, *ibid.*, this issue, page 7.

3. Gutmann, E.; Guttmann, L.; Medawar, P. B., and Young, J. Z.: The Rate of Regeneration of Nerve, *J. Exper. Biol.* **19**:14-44 (May) 1942.

Seddon, Medawar and Smith¹ that the process implied in the use of the term advances at a slower rate than does growth of the axon tips, which is revealed by the advance of Tinel's sign. The present findings, however, suggest that, though the processes in the two types of fibers (motor and sensory) may not be identical in nature, there is no significant difference in their rates of advance as calculated by the two methods. The figures given by Seddon and associates¹ also support this suggestion (1.6 ± 0.2 mm. per day for functionally mature motor fibers following suture and an average rate of 1.71 mm. per day for the progress of Tinel's sign following suture), though the authors themselves stated that "the wave front for Tinel's sign" should be "well in front of that for motor and sensory fibers that have advanced to functional maturity."

In a later, final, report⁴ on the rate of regeneration in human peripheral nerves, attention will be directed to the nature of the process which is being measured when the rate of regeneration is calculated, and to the significance of the various criteria on which the different methods depend.

SUMMARY

Observations on the rate of advance of Tinel's sign demonstrate that after suture in the proximal part of the limb regenerating sensory fibers advance at a progressively diminishing rate, which in the initial stages may be as great as 3 mm. per day. It gradually slows until it reaches a value of approximately 0.5 mm. per day over the terminal stages of recovery.

The National Health and Medical Research Council of Australia made a grant in aid of this investigation.

University of Melbourne.

4. Sunderland, S.: Rate of Regeneration in Human Peripheral Nerves and Analysis of Interval Between Injury and Onset of Recovery, *Arch. Neurol. & Psychiat.*, to be published.

RATE OF REGENERATION OF MOTOR FIBERS IN THE ULNAR AND SCIATIC NERVES

SYDNEY SUNDERLAND, M.D., D.Sc.
MELBOURNE, AUSTRALIA

IN A PREVIOUS paper¹ a method for estimating the rate of growth of functionally mature motor fibers in human peripheral nerves was reported, together with clinical observations on the course and rate of regeneration after lesions of the radial nerve. In the present paper, which deals with the rate of advance of motor fibers after lesions of the ulnar and sciatic nerves, the investigation was conducted as for the radial nerve, and reference should be made to the original paper for a detailed account of the method employed to calculate the rate and the criteria adopted in selecting the clinical material.

The rate of regeneration, R , in millimeters per day, is expressed by the formula:

$$R = \frac{L^2 - L^1}{T^2 - T^1}$$

L^1 and L^2 are the shortest distances to two muscles from a point on the nerve proximal to the site of origin of its branches. Values for these lengths were obtained for a series of muscles from an anatomic investigation of the ulnar and sciatic nerves.² The lengths were measured directly along the nerve and its branches between a selected point on the nerve and the site of entry of the branch into the muscle. If more than one branch supplied a muscle, the measurement selected was the shortest route available. The position of the point, however, is immaterial, since the distance along the nerve to the more proximally innervated muscle is common to the measurement for each muscle. For reasons detailed in the original paper, this formula should not be employed when a considerable distance separates the muscles. By the

From the Department of Anatomy and Histology, University of Melbourne.

1. Sunderland, S.: The Course and Rate of Regeneration of Motor Fibres Following Lesions of the Radial Nerve, *Arch. Neurol. & Psychiat.* **56**:133-157 (Aug.) 1946.

2. Sunderland, S., and Hughes, E. S. R.: The Metrical and Non-Metrical Features of the Muscular Branches of the Ulnar Nerve, *J. Comp. Neurol.* **85**:113-126 (Aug.) 1946; The Metrical and Non-Metrical Features of the Muscular Branches of the Sciatic Nerve and Its Medial and Lateral Popliteal Divisions, *ibid.* **85**:205-222 (Oct.) 1946.

selection of suitable muscles, the rate should be calculated independently over several short sections of the nerve. This reduces to a minimum inaccuracies due to (a) the fact that the rate normally diminishes as the axons advance and (b) variations in the delay occurring within a muscle before recovery appears.

T^1 and T^2 signify the times taken to reinnervate the two muscles, calculated in days from the date of injury or nerve suture to the date of the onset of recovery. To qualify for selection, it was necessary for the cases to fulfil the following conditions:

1. Interruption of conduction must be complete and associated with wallerian degeneration.

2. The onset and progress of recovery must be such as to suggest uniform involvement of the fibers at the site of injury.

3. The onset and progress of recovery must be such as to suggest that the axons had commenced to regenerate at about the same time.

4. Any departure from the normal order of recovery should be capable of satisfactory explanation on the basis of established anatomic variations.

5. In order to detect the earliest signs of recovery in individual muscles, the patients are to be examined at intervals not exceeding a week until all muscles are contracting. In 2 cases in which intervals of two to four weeks occurred between examinations, muscles showing recovery at the second examination were considered to have recovered midway between the two examinations. It is an advantage for all observations to be made by the same observer (as in the present inquiry), since this reduces the personal factor introduced by the transferring of patients from clinic to clinic.

Advantages of the method are (1) that it renders unnecessary a knowledge of the level of the injury and the initial delay before the commencement of regeneration and (2) that the rate of regeneration can be estimated separately over different segments of the nerve by selecting muscles which are innervated at different levels. By this means it is possible to ascertain whether or not regeneration proceeds uniformly during the entire process. It is not possible, however, to estimate the rate over the section of the nerve proximal to the origin of its first branch.

L and T are used throughout the text to signify L^2-L^1 and T^2-T^1 .

The rate of regeneration can be estimated in any individual case, or an average rate, calculated from mean readings for T , can be obtained from observations on a large series of cases. In an individual case it is necessary to take into consideration the considerable and unpredictable range of variation in the length of the shortest fibers to any given

muscle. This factor was apparently disregarded by Seddon, Medawar and Smith.³ When mean readings for L and T are obtained from a number of cases, as in the present inquiry, it is believed that this unpredictable element is reduced to a minimum. By taking average readings for L and T for any group of muscles, factors are disregarded which are peculiar to an individual case and which may influence the rate. Regardless of the method employed, however, the rate in any individual case can be calculated only in retrospect—that is, after regeneration has advanced over suitable lengths of the nerve. For this to be possible the length must be known, and there is no way of obtaining this in the living subject; recourse must therefore be made to the values provided by the cadaver, and these show a wide range of variation.

MATERIAL

The observations are based on a series of 106 lesions of the ulnar nerve and 67 lesions of the sciatic nerve (main trunk and medial and lateral popliteal divisions) occurring in 301 consecutive cases of peripheral nerve injuries which I studied over the period from 1941 to 1946 at an Australian military hospital and at the Repatriation Clinic, Melbourne. The case histories are to be reported in detail elsewhere. Of the series, only 21 lesions of the ulnar and 16 lesions of the sciatic nerve were suitable for the present inquiry.

ULNAR NERVE

The only muscles appropriately spaced to permit a calculation of the rate of regeneration by the use of the formula were the hypothenar group and the first dorsal interosseous muscle. Thus, the rate could be calculated only over the terminal portion of the nerve.

Distance.—The length, L , in each of 20 specimens is given in table 1. In the preliminary anatomic investigations, the distance was measured from the level of the tip of the styloid process of the radius to each of the three hypothenar muscles. Clinically, however, it was not always possible at the onset of recovery to detect which fibers of the group were contracting. For this reason, the hypothenar muscles have been considered as a single anatomic unit, and in arriving at a value for L (i. e., L^2-L^1) the shortest distance to the first hypothenar muscle to be supplied was taken as the distance to the group.

Time.—The onset of recovery in the hypothenar and the first dorsal interosseous muscles following axonotmesis (11 patients) and suture (10 patients), together with values for T , are given in table 2, which also contains details relating to the cause and the level of the injury. The mean and the standard deviation for T are given in table 5.

3. Seddon, H. J.; Medawar, P. B., and Smith, H.: Rate of Regeneration of Peripheral Nerves in Man, *J. Physiol.* **102**:191-215 (Sept. 30) 1943.

TABLE 1.—*Values for L² — L¹ (L)**

Specimen	H and D1	G and FDL	G and FHL	PL and EHL	TA and EHL
1.....	†	106	116	69	43
2.....	67	131	220	89	67
3.....	†	151	183	86	71
4.....	46	153	204	98	64
5.....	63	158	155	106	72
6.....	51	162	214	137	135
7.....	63	141	194	75	72
8.....	45	125	203	104	77
9.....	37	72	186	115	83
10.....	52	133	182	29	35
11.....	33	165	170	62	84
12.....	34	†	†	42	110
13.....	58	120	161	130	121
14.....	63	135	193	99	82
15.....	56	174	133	45	23
16.....	54	202	183	27	48
17.....	23	166	201	130	100
18.....	45	142	126	84	79
19.....	44	127	233	103	97
20.....	54	135	178	117	100
Mean.....	49	142	182	87	78
Standard deviation.....	12	28	31	33	28

* The distances (in millimeters) are based on measurements taken from the level of the tip of the styloid process of the radius for the ulnar nerve and from a level 5 cm. above the medial epicondyle of the femur for the sciatic nerve and its divisions. H indicates the hypothenar muscles; D1, first dorsal interosseous muscles; G, gastrocnemius; FDL, flexor digitorum longus; FHL, flexor hallucis longus; TA, tibialis anterior; PL, peroneus longus, and EHL, extensor hallucis longus.

† The first dorsal interosseous muscle was supplied partly or completely by the median nerve.

‡ In this specimen, the first branch of the gastrocnemius left the nerve above the 5 cm. level, so that values could not be obtained for these two sections on the same basis as for the others.

TABLE 2.—*Lesions of the Ulnar Nerve (Axonotmesis and Suture)*

Causative Injury; Nature of Nerve Injury	Case No.	Level of Injury, Mm.*	MHE to RSL, Mm.	Interval, in Days, Between Injury and Suture	Return of Voluntary Contraction, Weeks		T ² — T ¹
					H	D 1	
Axonotmesis							
Laceration.....	103	50 above RSL	20	32	12
	323	20 below RSL	8	20	12
Gunshot wound.....	30	200 above RSL	62	79	17
	31	100 above MHE	280	...	80	91	11
	129	60 above MHE	260	...	90	107	17
	136	170 above MHE	290	...	29	41	12
	179	80 above MHE	270	...	22	30	8
	237	80 above RSL	34	42	8
Gunshot wound + bone injury.....	43	130 above RSL	53	61	8
	176	140 above RSL	32	39	7
	235	10 above RSL	29	40	11
Suture							
Compound fracture of radius and ulna.....	328	150 above RSL	295	177	32	42	10
Laceration.....	105	250 above RSL	300	2	40	65	25
	139	10 above RSL	...	Immediate	28	51	23
	158	25 above MHE	275	104	85	109	24
	269	265 above RSL	290	277	46	62	16
	290	At MHE	250	1	81	102	21
	325	80 above RSL	...	5	40	54	14
Gunshot wound.....	38	80 above RSL	...	191	17	47	30
	207	60 above MHE	260	131	67	81	14
Gunshot wound + bone injury.....	243	90 above MHE	265	Immediate	37	55	18

* H indicates hypothenar muscles; D1, first dorsal interosseous muscle; RSL and MHE, levels of the styloid process of the radius and the medial epicondyle of the humerus, respectively.

Results.—The mean rate of regeneration was 0.6 mm. per day after “axonotmesis” and 0.4 mm. per day after suture.

In studying the influence of individual variations in L and T , it is reasonable to assume that high values for T ($T+$) would probably mean that the distance traveled was greater in that patient, while low values for T ($T-$) would probably be associated with shorter distances. Calculations made on this basis (using the standard deviations) for both types of lesions gave the following rates:

	L+ T+	L- T-
Following axonotmesis	0.6 mm. per day	0.7 mm. per day
Following suture.....	0.3 mm. per day	0.4 mm. per day

Comment.—Over the terminal portion of the nerve, functional regeneration proceeded at the rate of about 0.6 mm. per day after axonotmesis and 0.4 mm. per day after suture. The corresponding rates for the terminal portion of the radial nerve (posterior interosseous division) were 0.8 and 0.6 mm. per day. The interval, T , did not vary significantly with the level of the injury; apparently, the rate of growth for the terminal portion of the nerve is not influenced by the level of the injury; that it is related to the duration of the latent period intervening between the injury and the first appearance of recovery (after allowing for the influence of the level of the injury on this period) has been suggested by previous inquiries (Seddon, Medawar and Smith³; Sunderland¹). This matter will be more fully discussed in a subsequent report.

SCIATIC NERVE AND ITS MEDIAL AND LATERAL POPLITEAL DIVISIONS

The rate of regeneration was measured over the sections of the medial and lateral popliteal nerves representing the following levels of innervation: gastrocnemius to flexor digitorum longus; gastrocnemius to flexor hallucis longus; tibialis anterior to extensor hallucis longus, and peroneus longus to extensor hallucis longus. These sections cover what might be regarded as the intermediate portion of the sciatic nerve.

Distance.—The length, L , for each of these sections in 20 specimens is given in table 1.

Time.—The onset of recovery following axonotmesis (15 patients, presenting 16 lesions—in case 245 the lesion was bilateral) in the different muscles concerned and information relating to the cause and the level of the injury are given in table 3. Values for T are given in table 4.

Results.—The mean rates of regeneration, calculated in millimeters per day, over the selected sections of the nerve are given in table 5; the estimated rates for the high and low values (standard deviations), of the lengths and times, respectively, are also included.

TABLE 3.—*Lesions of the Sciatic, Medial Popliteal and Lateral Popliteal Nerves (Axonotmesis)*

Nature of Causative Injury	Case No.	Level of Injury, Mm.	Return of Voluntary Contraction, Weeks *					
			G	FDL	FHL	TA	PL	EHL
Simple compression.....	188	Neck of fibula	21	21	36
	245	Neck of fibula	24	20	36
	245	Neck of fibula	18	18	30
Simple fracture of femur.	326	100 above MFE†	29	46	53	43	44-48	49
Gunshot wound.....	82	Head of fibula	18	18	35
	88	Lower third of thigh..	102	111	111
	95	50 above MFE	15	24	29	24	19	33
	109	70 above MFE	13	21	21	13	13	21
	112	230 above MFE	26	33	41	28	28	23
	145	160 above MFE	18	37	42	27	27	36
	190	At MFE	22	42	42
	240	150 above MFE	37	31	44
	254	Head of fibula	7	7	12
Gunshot wound + bone injury.....	150	Midthigh	13	13	21
	260	50 above MFE	12	35	35
	293	Midthigh	71	59	80

* G indicates gastrocnemius; FDL, flexor digitorum longus; FHL, flexor hallucis longus; TA, tibialis anterior; PL, peroneus longus, and EHL, extensor hallucis longus.

† MFE indicates medial epicondyle of the femur.

TABLE 4.—*Values for $T^2 - T^1$ (T)*

Nature of Causative Injury	Case No.	Times, in Weeks *			
		G and FDL	G and FHL	TA and EHL	PL and EHL
Simple compression.....	188	15	15
	245	12	16
	245	12	12
Simple fracture of femur.....	326	17	24	6	3
Gunshot wound.....	82	17	17
	88	9	..
	95	9	14	9	14
	109	8	8	8	8
	112	7	15	5	5
	145	19	24	9	9
	190	20	20
	240	7	13
	254	5	5
Gunshot wound + bone injury	150	8	8
	260	23	23
	293	9	21
Mean.....		14.7	18.3	9.4	11.2
Standard deviation.....		6.5	6.1	3.5	5.4

* G indicates gastrocnemius; FDL, flexor digitorum longus; FHL, flexor hallucis longus; TA tibialis anterior; PL, peroneus longus, and EHL, extensor hallucis longus.

Comment.—Since the regenerating nerve fiber advances at a diminishing rate, the distance over which the rate is calculated should be sufficiently short to reduce or eliminate the influence of this factor. In the case of the two sections (*a*) gastrocnemius to flexor digitorum longus and (*b*) gastrocnemius to flexor hallucis longus, it is believed that the discrepancy in the rates could be due to the long distances involved in the calculations. Against this, however, is the observation that when the lengths L , $L+$ and $L-$ for both sections are arranged in numerical order, the corresponding rates do not progressively decrease as the length increases but show certain conflicting irregularities; the fastest rate is, however, associated with the shortest distance. In the case of the two sections of the nerve, (*a*) tibialis anterior to extensor

TABLE 5.—Rates of Regeneration, in Millimeters per Day

Nerve Segment over Which Rate Was Estimated *	Distance, L , in Mm.	Time, T , in Weeks	Mean Rate Calculated from Mean L and T	Rate Estimated from $L+$ and $T+$ †	Rate from $L-$ and $T-$ †
Ulnar nerve					
H and D 1.....	49 ± 12				
Axonotmesis.....	11.2 ± 3.4	0.6	0.6	0.7
Suture.....	19.5 ± 6.1	0.4	0.3	0.4
Sciatic nerve					
Axonotmesis					
G and FDL.....	142 ± 28	14.7 ± 6.5	1.4	1.1	2.0
G and FHL.....	182 ± 31	18.3 ± 6.1	1.4	1.2	1.8
TA and EHL.....	78 ± 28	9.4 ± 3.5	1.2	1.2	1.2
PL and EHL.....	87 ± 33	11.2 ± 5.4	1.1	1.0	1.3

* H indicates hypothenar muscles; D 1, first dorsal interosseous muscles; G, gastrocnemius; FDL, flexor digitorum longus; FHL, flexor hallucis longus; TA, tibialis anterior; EHL, extensor hallucis longus, and PL, peroneus longus.

† $L+$ and $T+$ indicate high values, and $L-$ and $T-$ low values, for length and time.

hallucis longus and (*b*) peroneus longus to extensor hallucis longus, the shorter distances no doubt account for the more consistent results.

In view of the possible sources of error, the only justifiable conclusion is that regeneration in the intermediate section of the sciatic nerve (just below the knee) occurs at a rate which diminishes from 2 to 1 mm. per day. These values agree with the rates for the radial nerve at and just below the elbow.

SUMMARY

An investigation of the rate of functional regeneration of motor fibers following interruption of conduction in the ulnar and sciatic nerves provided the following results:

1. For the terminal section of the ulnar nerve in the hand, the rate of growth was 0.6 mm. per day after axonotmesis and 0.4 mm. per day after suture.

2. For the section of the sciatic nerve just below the knee, the rate of growth after axonotmesis diminished from 2 to 1 mm. per day.

The National Health and Medical Research Council of Australia provided a grant in aid of this investigation.

University of Melbourne.

NEUROPSYCHIATRIC MANIFESTATIONS DURING THE COURSE OF MALARIA

Experiences in the Mediterranean Theater in World War II

BENJAMIN BOSHERS, M.D.

CHICAGO

MALARIA is one of the most widespread and prevalent diseases known to man. The armed forces of the United States encountered this infection in its various forms in many parts of the world. Many thousands of the military personnel were treated successfully for tertian, quartan or malignant tertian infection. In unknown thousands the disease was suppressed by the quinacrine (atabrine)-quinine prophylactic regimen, so that to date there has been no clinical evidence of the infection. It may be expected that with return of the troops to the United States cases of malaria will appear in nonendemic zones as well as in endemic areas. This is because those who have had the disease will have recurrences. Nocht and Mayer¹ pointed out that tertian malaria may recur up to five years in a nonendemic zone and malignant tertian malaria up to two years, and that quartan malaria may lie dormant for years. Furthermore, the previously suppressed disease may become activated. The greater number of patients with symptomatic malaria, as well as the asymptomatic gametocyte carriers, will act as a source of infection for susceptible civilians in areas in which the anopheles mosquito is found. Since malaria is recognized as a disease of protean manifestations, all physicians will have to be on the alert for the plasmodium as the cause of various atypical pyrexial syndromes. Some forms of the disease may even run an afebrile course for some time. Neuropsychiatrists, particularly, will have to watch for the cerebral manifestations.

A review of the literature suggests that malaria with cerebral symptoms is due essentially to *Plasmodium falciparum*. For example, Nocht and Mayer stated: "With few exceptions, comatose forms occur only in malignant tertian infections." However, in a series of 6,059 cases of malaria in a United States Army general hospital in India,² cerebral malaria occurred in 140 cases, or 2.3 per cent. Of the latter group,

Read before the Section on Neurology and Psychiatry at the Ninety-Fifth Annual Session of the American Medical Association, San Francisco, July 4, 1946.

1. Nocht, B., and Mayer, M.: *Malaria: A Handbook of Treatment, Parasitology and Prevention*, London, John Bale, Sons & Curnow, Ltd., 1937.

2. Fitz-Hugh, T., Jr.; Pepper, D. S., and Hopkins, H. O.: *The Cerebral Form of Malaria*, Bull. U. S. Army M. Dept., December 1944, no. 83, pp. 39-48.

Plasmodium vivax was the causative organism in 5, as against *P. falciparum* in 88. Nine cases of the cerebral form were seen in a total of 1,155 cases of malaria in the Mediterranean Theater.³ In 2 of the 9 cases the causative organism was that of tertian malaria; in 6, *P. falciparum*. In 1 case no organism was found. The Russians⁴ have been much interested in a fulminating form of tertian malaria which attacks children and youths in central Russia. The syndrome is that of an acute, overwhelming infection of the central nervous system, rapidly fatal in a few hours. In 12 of 17 cases examination revealed *P. vivax*. It becomes imperative, therefore, that one's thinking be flexible as regards the causative organism in malaria. A recent case report from the Veterans Hospital Administration⁵ is in point. The patient was psychotic for three weeks in the hospital before the occurrence of chilly sensations and a temperature of 102 F. caused a search for the plasmodium. *P. vivax* was isolated from the smear, and the patient recovered with specific therapy.

The lesions of cerebral malaria have been well described. Thus, Cerletti⁶ pointed out the choking of the blood vessels by the parasites, injury to the vessel walls by the toxins, perivascular changes and formation of new vessels. The leptomeninges show high grade changes. Both the ectodermal and the mesenchymal elements of the brain are involved with ganglion cell disease and hemorrhages into the white substance. Rigdon and Fletcher⁷ also described a cellular reaction, with the formation of "malaria nodules" in the cerebrum and the cerebellum. These may be relatively avascular (Dürck's granuloma) or may be associated with hemorrhages. The distribution and nature of the lesions, according to these authors, suggest that the pathologic basis is cerebral anoxia. That the aforementioned lesions are not exclusively the product of *P. falciparum* may be seen in the report from the King Edward VII Memorial Hospital in Bombay.⁸ In many of the cases reported here the disease was diagnosed as meningitis,

3. Horn, H., and Karelitz, S.: Clinical Experience with Malaria at a General Hospital During Summer and Fall of 1943, *M. Bull. North Africa Theat. Op.* (no. 4) 1:2-11 (April) 1944.

4. Tarejev, E. M.; Gontseva, A. A., and Rotenburg, S. S.: Fulminating Type of Tertian Malaria, *Sovet. med.* (no. 4) 7:12-14, 1943; abstracted, *Trop. Dis. Bull.* 41:257-258 (April) 1944.

5. Singleton, D. E.: Psychosis with Malaria, *M. Bull. Vet. Admin.* 21:109-110 (July) 1944.

6. Cerletti, U.: Die histopathologischen Veränderungen der Hirnrinde bei Malaria perniciosa: Beiträge zur Kenntnis der akuten Rindenerkrankungen, in Nissl, F., and Alzheimer, A.: *Histologische und histopathologische Arbeiten über die Grosshirnrinde*, Jena, G. Fischer, 1910-1911, vol. 4, pp. 169-226.

7. Rigdon, R. H., and Fletcher, D. E.: Lesions in the Brain Associated with Malaria: Pathologic Study on Man and on Experimental Animals, *Arch. Neurol. & Psychiat.* 53:191-198 (March) 1945.

typhoid and pneumonia. In 33 instances the parasite was isolated: *P. falciparum*, 24 cases; *P. vivax*, 7 cases; mixed infection, 1 case. Edema, vascular thrombosis and hemorrhages were observed. Granulomas were noted in the brains of patients who did not die quickly. The authors pointed out that the parasitized cells tend to agglutinate and to adhere to the vessel wall; the endothelial cells proliferate, and thrombosis ensues. Diapedesis of red cells and focal necrosis occur. If the patient recovers, the neuroglia proliferate and microglial cells invade the field. The end result is a patch of sclerosis, multiple areas of which may produce considerable alteration of neural function. The authors emphasize that the failure to find parasites in the peripheral blood does not rule out cerebral malaria. In some of their cases smears failed to yield the organism.

With lesions present in all parts of the central nervous system, meninges, blood vessels and parenchyma, the variable presenting syndrome of so-called cerebral malaria may be studied. Certainly, the concept of a "comatose" form only is misleading. In a series of 12 cases of cerebral malaria at a United States naval base hospital, Simpson and Sagebiel⁹ described a sudden onset with epileptiform convulsions and coma in 9. Status epilepticus was common. In 4 cases there were signs of meningitis. Acute confusional psychosis developed in 6 cases, with lucid intervals. Pleocytosis, with a count of 30 to 165 cells per cubic millimeter of cerebrospinal fluid, was observed. Others have variously described the clinical syndrome as "cerebral," with symptoms simulating coma, encephalitis, tetanus, epilepsy or meningitis, or as "masked," with symptoms simulating trigeminal neuralgia, migraine, neuritis, aphasia or psychotic episodes.¹ In addition, paralysis of any type, hemianopsias or a bulbar and cerebellar syndrome may occur, the patient thus presenting various neurologic and psychiatric entities. The original diagnosis may well be epilepsy, meningitis, cerebral tumor, encephalitis, cerebrovascular accident or mental disturbance.¹⁰ Arbuse¹¹

8. Dhayagude, R. G., and Purandare, N. M.: Autopsy Study of Cerebral Malaria with Special Reference to Malarial Granuloma, *Arch. Path.* **36**:550-558 (Dec.) 1943; abstracted, *Trop. Dis. Bull.* **41**:533-535 (July) 1944.

9. Simpson, W. M., and Sagebiel, J. L.: Cerebral Malaria: A Report of Twelve Cases Encountered at U. S. Naval Base Hospital, *U. S. Nav. M. Bull.* **41**:1596-1602 (Nov.) 1943.

10. Kneedler, W. H.: Symposium on Tropical Medicine: Malignant and Atypical Malaria, *Clinics* **2**:809-827 (Dec.) 1943. Brill, N. Q., and Pellicano, V. L.: Estivoautumnal Malaria with Frontal Lobe Syndrome, *J. A. M. A.* **121**:1150-1152 (April 3) 1943. McGinn, S., and Carmody, J. T. B.: Cerebral Symptoms in Malaria, *U. S. Nav. M. Bull.* **43**:1157-1162 (Dec.) 1944. Hyman, A. S.: Clinical Masquerades of Malaria: Observations in the South Pacific Combat Areas, *ibid.* **45**:287-303 (Aug.) 1945. Eckstein, A.: Malaria und Zentralnervensystem im Kindesalter, *Ann. pædiat.* **168**:65-96, 1942.

11. Arbuse, D. I.: Neuropsychiatric Manifestations in Malaria, *U. S. Nav. M. Bull.* **45**:304-309 (Aug.) 1945.

pointed out that, in addition to the focal lesions in the substance of the central nervous system, neuritis of the optic nerve and the abducens, facial, ulnar and peroneal nerves, as well as the brachial plexus, has been observed. Paraplegias due to involvement of the spinal cord have been seen. Arbuse raised the question of the validity of considering polyneuritis a complication of malaria, since the latter occurs in areas where beriberi is prevalent. He expressed the opinion that latent beriberi may be activated by malaria. He classified the neuropsychiatric manifestations as (1) those presenting meningitis, with slight focal or generalized neurologic signs; (2) those with definite localizing significance, such as apoplectic phenomena, coma and convulsions, and (3) those referable to the spinal cord and peripheral nerve. Horn and Karelitz,³ describing cases from the Mediterranean Theater, raised the question whether their 4 patients with herpes zoster and the 3 with meningoencephalitis did not have an intercurrent virus infection activated by the malaria. However, the known pathologic lesions of cerebral malaria would be consonant with a clinical picture of meningoencephalitis; and herpetic lesions, particularly the labial form, were the rule, even in uncomplicated cases. It is unnecessary, therefore, to invoke an etiologic agent other than the plasmodium and its by-products.

In assessing some of the psychotic reactions incident to malaria, the role of the medication must be determined. This is not always possible, because many patients, particularly children, become disturbed during protracted periods of high fever. In addition, the toxic-exhaustive effects of repeated, or even of a single, attack of malaria are not to be denied. However, there are a sufficient number of cases of toxic responses to quinacrine with psychotic manifestations to make one investigate the subject. In a chronic experiment in cats, Pick and Hunter¹² were able to show that quinacrine produced a central depressant action, the degree depending on the content of drug in the brain, and not in the blood. Scudi and his co-workers¹³ demonstrated that experimentally quinacrine produces irritation of the gastrointestinal tract, with diarrhea, hemoconcentration and loss of blood chlorides and blood bicarbonates. Large doses produce necrosis of the liver. The toxic effect can be increased by fasting the animals or prevented by feeding them a high protein and low fat diet. Thompson¹⁴ treated

12. Pick, E. P., and Hunter, J.: Action of Atabrine on Electrocortico Potentials, *J. Pharmacol. & Exper. Therap.* **80**:354-361 (April) 1944.

13. Scudi, J. V.; Jelinek, V. C., and Kuna, S.: Biochemical Aspects of the Toxicity of Atabrine: Acute Effects of Massive Doses in Rat, *J. Pharmacol. & Exper. Therap.* **80**:144-149 (Feb.) 1944. Scudi, J. V., and Hamlin, M. T.: Biochemical Aspects of the Toxicity of Atabrine: II. Influence of Diet upon Effects Produced by Repeated Doses of the Drug, *ibid.* **80**:150-159 (Feb.) 1944.

14. Thompson, J. H.: Large Initial Doses of Atabrine in the Treatment of Benign Tertian Malaria, *J. Trop. Med.* **47**:61-64 (Dec.-Jan.) 1944-1945.

100 patients with relapses and latent benign tertian malaria. In patients given an initial dose of 0.6 Gm. of quinacrine hydrochloride, then 0.2 Gm. three times a day for six doses, then 0.1 Gm. three times a day for one week, no toxic symptoms developed. Four of 8 patients taking 1.0 Gm. had nausea. One man had "strange thoughts running through his head," which cleared up as the disease subsided. Lerro¹⁵ reported 2 cases of neuropsychiatric complications which disappeared immediately when the drug was discontinued. This has been the experience of many others.¹⁶ Bispham¹⁷ studied 49,681 patients receiving quinacrine therapy. Of the 38 patients showing toxic symptoms of all types, varying from gastrointestinal disturbances and simple headache to severe psychosis, all had prompt clearing of their symptoms as soon as the drug was stopped. In evaluating reports from the Malay States, India and China, Nocht and Mayer¹ (page 52) pointed out the extremely low incidence of neuropsychiatric reactions, e. g., 2 cases of temporary delirium in 750 cases and 2 cases of depression in 1,200 cases. All workers describing large numbers of cases are agreed on the very low frequency of toxic cerebral reactions and the prompt reversibility when the drug is removed.

These observations are in keeping with the experience of my colleagues and myself. We were in contact with tens of thousands of soldiers taking quinacrine as suppressive treatment, 0.4 Gm. per week. Large numbers of patients over a period of almost three years were treated for malaria in the general hospital with which we were associated, but not a single case of quinacrine psychosis was encountered. Our introduction to quinacrine prophylaxis during the final phases of the Tunisian campaign, in the spring of 1943, was dramatic. The incidence of incapacitating vomiting and diarrhea was very high for three or four days. Patients and medical personnel were equally affected. The performance was not repeated in 1944 or 1945 when quinacrine therapy was resumed. Why the toxic response to the 1943 batch of quinacrine was so widespread has never been explained. Many patients turned a yellow-green from intake of the drug, but there was no concomitant toxic effect. The color disappeared on discontinuance of the drug.

In the Mediterranean Theater the incidence of cerebral malaria was comparatively low. The frequency of infections with *P. falciparum* fell off after the North African and Sicilian campaigns. In the Horn and

15. Lerro, S. J.: Report of Two Cases of Toxicity to Atabrine, *Mil. Surgeon* **89**:668-670 (Oct.) 1941.

16. Mental Symptoms Following the Use of Atabrine, editorial, *J. A. M. A.* **121**:765 (March 6) 1943. Ayala, F., and Bravo, G.: Psychosis Observed in the Treatment of Malaria with Atepe, *Rev. clín. españ.* **7**:70-72 (Oct. 15) 1942.

17. Bispham, W. N.: Toxic Reactions Following the Use of Atabrine in Malaria, *Am. J. Trop. Med.* **21**:455-459 (May) 1941.

Karelitz³ series of 1,155 cases, in the summer of 1943, 39.1 per cent were of the benign tertian variety and 33.7 per cent of the malignant type. The cases came from Sicily and the Eastern Base Sector of the North-African Theater, the Tunis-Bizerte Sector. Estivoautumnal malaria was exceedingly uncommon in Italy. Golz¹⁸ pointed out that in 75 per cent of the cases reported between November 1942 and March 1945 the malaria was of the *P. vivax* variety and in 10 per cent of the *P. falciparum* group, and that the latter were a product of the early days of Tunisia and Sicily. These data reflect our experience, despite the fact that malaria was the greatest single cause of hospitalization in the Theater, and that the malaria rate often exceeded the figure for battle casualties by as much as 20 per cent.

The cases that were presented to the neuropsychiatrist, especially when the Italian campaign was under way, were the bizarre, the atypical—in short, the type of case I am trying to point out as a “State-side” challenge. The psychiatrist was often called to see a patient with a bursting headache, severe retro-orbital pain and backache. No focal or meningeal signs could be elicited, but the advent of a typical or atypical febrile course would lead to a series of “malaria slides” being made, with the result that the diagnosis was readily established. However, if the patient entered with a diagnosis of “epilepsy,” “suspected cerebellopontile angle tumor” or “psychosis unclassified” and he was afebrile, the problem was more difficult. The routine practice of making a thick and a thin blood smear for every patient who became febrile, no matter how mildly, helped to establish the presence of malaria. The importance of obtaining repeated smears, thick and thin, at several intervals of the day, preferably several hours after the paroxysm, is emphasized.

The vagaries of symptoms in an atypical case of cerebral malaria are seen in the following presentation:

History.—L. J. B., a staff sergeant aged 26, fighter squadron in Italy, became ill Oct. 6, 1944, with nausea and some vomiting. That afternoon he began to “shake.” No further history could be elicited. The temperature was 97 F., the pulse rate 104 and the respiratory rate 24. There were no abnormal findings, but the patient was apprehensive, resistive and incoherent. The battalion surgeon who had sent the patient into the station hospital, on Oct. 7, expressed the opinion that the patient might have malaria because the temperature was 100.2 F. at the time of onset. Two smears were negative for malaria.

The patient was semicomatose on October 8. Lumbar puncture done on that day revealed elevated pressure, with 84 cells per cubic millimeter, 30 polymorphonuclear leukocytes and 54 lymphocytes. The medical officer considered the diagnosis of choriolymphocytic meningitis or encephalitis. On October 11 the patient had four generalized convulsions.

18. Golz, H. H.: The Diagnosis and Treatment of Malaria, *M. Bull. Mediterranean Theat. Op.* 3:103-111 (April) 1945.

Examination.—He was transferred to our general hospital with the diagnosis of "epilepsy" and was received on October 11, in deep coma. There was considerable motor unrest but no movements of the limbs on the right side. Examination was difficult but revealed ankle clonus bilaterally, Babinski and Oppenheim signs and absence of abdominal reflexes. The right side of the face did not move as well as the left. There was a slight internal squint of the right eye. Pendular nystagmus was present on looking ahead. This changed to a definite slow vestibular type on looking to the right. Conjugate movements of the eyeballs were preserved. The pupils dilated to darkness and reacted poorly to light. The fundi were normal. The patient did not respond to painful stimuli. Definite nuchal indications of meningitis, with a direct Brudzinski sign and a bilateral Kernig sign, were present. The temperature was 102.2 F., the pulse rate 96, the respiratory rate 22 and the blood pressure 126 systolic and 80 diastolic.

The picture was that of acute meningoencephalitis. How many of the focal signs were due to the illness per se and how many were the product of the postconvulsive state could not be determined then.

Spinal puncture yielded clear fluid, under a pressure of 280 mm. of water, with normal dynamics. Examination revealed 4 white cells (lymphocytes) per

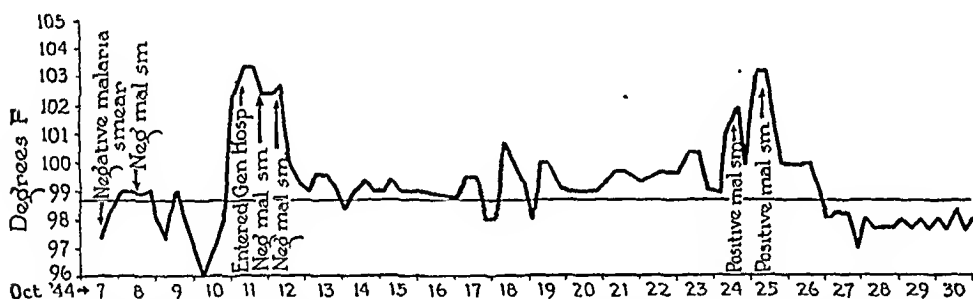


Fig. 1.—Temperature chart in a case of malaria with cerebral complications due to *Plasmodium vivax*.

cubic millimeter; 100 mg. of sugar and 733 mg. of chlorides, per hundred cubic centimeters, and a negative reaction for globulin. The total protein was 22 mg. per hundred cubic centimeters. The Kahn reaction was negative. The colloidal gold curve was 1111000000. A subsequent smear, culture and pellicle test all failed to reveal the parasites.

Course in Hospital.—The temperature dropped to normal on October 12. The patient responded to questions but was confused much of the time. Neurologic signs persisted.

October 13: Spinal puncture revealed that the spinal fluid was clear and under a pressure of 260 mm. of water. The pressure dropped to 70 mm. of water after removal of 30 cc. of fluid. Examination revealed 5 white blood cells (lymphocytes) per cubic millimeter, and 62 mg. of sugar (simultaneous blood sugar level, 84 mg.) and 759 mg. of chlorides per hundred cubic centimeters. The reaction for globulin was negative, and the total protein was 24 mg. per hundred cubic centimeters. Smear and subsequent culture did not reveal parasites. That day a generalized convulsion occurred and then a jacksonian fit on the right side; an attack of "status epilepticus" was aborted with intravenous injection of sodium amytal.

October 14: Right homonymous hemianopsia, transient, was suspected; there were periods of delirium and hallucinations. The patient was afebrile.

October 16: Two attacks of furor, epileptic equivalents, occurred.

October 17: The patient showed right homonymous hemianopsia (fig. 2 A). There was no astereognosis. A tendency toward perseveration was evident. Meningeal signs persisted.

October 17 to 24: The condition was essentially unchanged. The patient was somewhat confused. The right hemianopsia persisted (fig. 2 B).

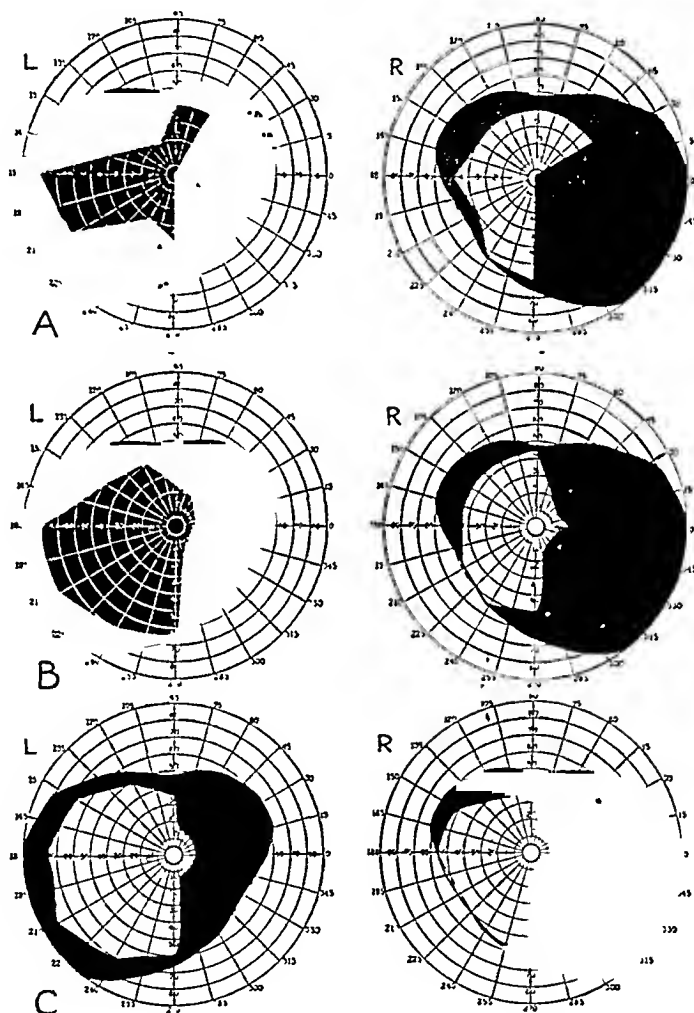


Fig. 2.—Visual fields in a case of malaria with cerebral complications due to *Plasmodium vivax*. A, fields on Oct. 17, 1944; B, fields on October 22, and, C, fields on October 30.

October 24: The temperature rose to 101.8 F. A smear of the blood revealed *P. vivax*.

October 25: The temperature rose to 103.4 F. during the morning. A second slide showed malarial parasites (*P. vivax*). Administration of quinine sulfate, 15 grains (0.975 Gm.) three times a day by mouth, was started.

Studies of the Blood.—Four smears made prior to October 24 had been negative for malaria parasites, and the patient had been afebrile for days when the organism was found. The white blood cell counts were as follows: October 7: 12,350 (neutrophils 80 per cent, lymphocytes 20 per cent); October 8: 5,300 (neutrophils 74 per cent, lymphocytes 26 per cent); October 11: 20,600

(neutrophils 89 per cent, lymphocytes 11 per cent); October 16: 4,300 (neutrophils 46 per cent, lymphocytes 54 per cent); October 25: 11,500 (neutrophils 64 per cent, lymphocytes 36 per cent).

Serologic Studies: The Kahn reaction of the blood was positive on October 11; the Kahn and Wassermann reactions of the blood were negative on October 17; all Kahn reactions of the spinal fluid were negative.

Special Laboratory Studies (October 25).—The blood bromide level was 75 mg. per hundred cubic centimeters.

Spinal puncture revealed a pressure of 200 mm. of water; 2 white blood cells (lymphocytes) per cubic millimeter, and 56 mg. of sugar, 685 mg. of chlorides and 26 mg. of total protein, per hundred cubic centimeters. The colloidal gold curve was 111100000.

Subsequent Course.—The patient was afebrile on October 26 and has been so since. He was normal mentally. All neurologic signs cleared up except the right homonymous field defect, which was still present when he was transferred to another general hospital, on Nov. 1, 1944.

Diagnosis.—The diagnosis was severe tertian malaria, with meningoencephalitic manifestations.

Studies of the blood and spinal fluid at the Army virus laboratory revealed that there was no neutralization of any of the known neurotropic viruses.

COMMENT

This man's illness started with a chill and low grade fever. Malaria was suspected, but two smears were negative for the parasites. The rapid onset of symptoms of meningoencephalitis with changes in the spinal fluid indicative of meningitis raised the question of a virus infection. However, the occurrence of the convulsions caused the diagnosis to be changed to "epilepsy." The presence of coma, a brain stem syndrome, in the presence of a temperature of 102.2 F. and meningeal signs ruled against the diagnosis of epilepsy. A normal cerebrospinal fluid and an afebrile course for many days did not help in the diagnosis. Two more smears were negative for malarial parasites. Evidence of transient focal disturbances in the brain was always present. On October 13 there occurred a generalized convulsion and then jacksonian fits on the right side. The next day transient right homonymous hemianopsia appeared, with periods of delirium and hallucinations. Epileptic equivalents, furor states, made an appearance, and, finally on October 17, a right homonymous hemianopsia became evident and persisted. All but the last symptom cleared up promptly when he was placed under quinine therapy. As often occurs in these cases, there was a transient positive reaction of the blood to the Kahn test. *P. vivax* was isolated on two occasions, and virus studies of the blood and the spinal fluid drawn during the acute illness gave negative results. The case was therefore unquestionably one of malarial meningoencephalitis with multiple neuropsychiatric manifestations.

Treatment was in accordance with current practice. Since the patient could swallow, he was given quinine by mouth. Quinacrine

would have worked as well. Had he been in deep coma and severely ill, we should have administered 0.6 Gm. (10 grains) of quinine dihydrochloride intravenously in 200 to 300 cc. of isotonic solution of sodium chloride, injecting it very slowly. This procedure could be repeated in three to four hours, but it was the policy of the Army¹⁹ to anticipate the need by giving intramuscular injections of quinacrine dihydrochloride, 0.2 Gm. (3 grains) in 5 cc. of sterile water in each buttock, a total of 0.4 Gm. (6 grains). As soon as the patient was conscious, the oral administration of quinacrine or quinine could be started.

The usual supportive measures—fluids and anticonvulsants, such as sodium amytal given intravenously—were utilized. (Patients in medical shock or with low blood counts were given transfusions, liver extract or iron, as needed.) After the patient was clinically well, the usual suppressive measures were again instituted. The patient had failed to take the prophylactic dose of quinacrine dihydrochloride for several weeks before he became ill with the infection.

CONCLUSIONS

1. Malaria was a common disease in the American armed forces in the Mediterranean Theater of Operations.

2. Neuropsychiatric complications simulating meningitis, encephalitis, epilepsy, cerebral tumor, vascular lesions and psychiatric disorders were encountered.

3. "Cerebral" forms of malaria were not limited to the disease caused by *P. falciparum*, but *P. vivax* and mixed infections could produce these pictures.

4. Quinacrine (atabrine) proved to be an effective nontoxic suppressive and active antimalarial drug.

ADDENDUM.—Since this article was written, two papers have appeared, one²⁰ describing toxic psychoses associated with the administration of quinacrine, and another²¹ setting forth the histopathologic changes in cerebral malaria as related to psychotic sequelae.

30 North Michigan Avenue.

ABSTRACT OF DISCUSSION

DR. W. McD. HAMMON, Berkeley, Calif.: This presentation is timely. I wish merely to emphasize that a great variety of unusual manifestations due to relapsing malaria may occur among returned servicemen during the next few years.

19. Treatment of Clinical Malaria and Malarial Parasitemia, United States War Department, Technical Bulletin (TB Med 72), Washington, D. C., Government Printing Office, July 10, 1944.

20. Sheppeck, M. L., and Wexberg, L. E.: Toxic Psychoses Associated with Administration of Quinacrine, *Arch. Neurol. & Psychiat.* 55:489-510 (May) 1946.

21. Arieti, S.: Histopathologic Changes in Cerebral Malaria and Their Relation to Psychotic Sequels, *Arch. Neurol. & Psychiat.* 56:79-104 (July) 1946.

Fortunately, there will be far fewer relapses of malaria due to *P. falciparum*, which is more likely to be associated with bizarre localized lesions, cerebral as well as others, than malaria of the *P. vivax* type; but, as Dr. Boshes has pointed out, the latter type is not always free from such complications.

Malaria from the Pacific areas, which I was fortunate enough to see both here in San Francisco and on Okinawa, presented a picture similar to that in the Mediterranean area. Severe psychoses; mild psychoneuroses of both short and long duration, and motor disturbances, including convulsions, encephalitis and meningismus, were among the manifestations noted. The occurrence of any of these symptoms in a veteran should raise the question of malaria in the mind of the physician, and one or two negative blood smears, particularly if examined by inexperienced technicians, should not eliminate that possibility. One should not be misled by the patient's statement that he has never had malaria and has now gone without quinacrine for several months, or even a year. Although most infected persons in whom the *P. vivax* parasites have been suppressed by quinacrine exhibit clinical malaria within a few weeks after stopping the drug, much longer intervals are by no means rare. Neither is it safe to generalize and to conclude that since a patient has not had a relapse in six or eight months he is cured.

I have observed several cases of acute malaria here, in the Pacific and in Africa in which the illness was first diagnosed as virus encephalitis, poliomyelitis or trypanosomiasis. Two such infections may exist concurrently, and the malaria parasites demonstrated may be only a manifestation of a latent, inactive, phase or of a clinical "bout" precipitated by the primary condition. Although I believe it unlikely, one cannot deny that the illness in the case presented by Dr. Boshes may have begun as a self-limited encephalitis of unknown origin, and not as malaria. At this stage of the disease malaria parasites were not observed. As spontaneous recovery was about to occur, the patient had an attack of malaria, accounting for the late rise in temperature and the observed parasitemia, which, in turn, yielded to specific therapy. The first infection could have accounted for the "break through" of the malaria. I recall the case of a paralyzed child in Costa Rica which was presented to me as one of cerebral malaria with permanent residual manifestations. The proof offered was that parasites were demonstrated and that the temperature fell after administration of quinine. The residual symptoms, however, were asymmetric flaccid paralyses, not unlike those of poliomyelitis.

I do not mention these cases to throw doubt on the diagnosis in the case presented, which is probably correct. I desire simply to emphasize that cerebral malaria can mimic closely other diseases. Physicians in this country think first, of course, of more common domestic disturbances, and physicians in the tropics think first of malaria and may miss other diagnoses. Since highly effective therapeutic agents are available for malaria, one must not fail to consider their use in appropriate cases.

DR. MEYER A. ZELIGS, Cincinnati: The importance of properly recognizing the protean manifestations of malaria, which during the war was primarily a problem of military medicine, is now a matter of concern to all physicians. When it is realized that tens of thousands of war veterans are now at large throughout the country, the social and medical aspects of this disease rank among the foremost postwar problems.

Dr. Boshes' experiences with this disease in the Mediterranean Theater would indicate that the central nervous system may be seriously involved even in cases of the benign tertian form. He has emphasized that the occurrence of cerebral manifestations during the course of the disease is not limited exclusively to the malignant tertian (*P. falciparum*) form of malaria and has pointed out the remarkable frequency of cerebral involvement in patients with benign tertian (*P. vivax*) infections. Fortunately, this has not been my experience. Out of a total of 2,500 Marines returned from the South Pacific with benign tertian malaria who were studied at Klamath Falls, Ore., for periods varying from three months to as long as a year, my colleagues and I saw no cerebral manifestations at any time. I wonder, therefore, whether the parasite in the cases which Dr. Boshes saw in the Mediterranean Theater may not have been of a different strain from that in the South Pacific Theater. Or is it possible that the rigors and physical fatigue associated with the combat situation so altered the bodily economy as to allow the parasites of benign malaria to produce what is ordinarily regarded as malignant manifestations? It is interesting in this regard that in our studies at Klamath Falls, we found that many malarial patients who had just been returned from combat with the diagnosis of "postmalarial asthenia," when carefully and deliberately appraised, were shown to have concomitant infections, such as amebiasis or hookworm, and that when these infections were specifically treated the "asthenic" state cleared dramatically. Many men with combat neurosis were also considered to be asthenic because of their recurrent malaria. With proper psychotherapy, however, and an appropriate rehabilitative program, these patients recovered from their asthenia most gratifyingly.

Dr. Boshes mentioned a distressing symptom—headache. We found that 15 to 20 per cent of men with a history of recurrent malaria were subject to frequent bouts of mild to severe headache. In fact, we soon realized that this symptom in itself was one of the most disturbing features of the interval phase of this disease. This "malarial headache" was most often present on arising in the morning and usually improved after the patient had been up a few hours. An almost characteristic feature of patients with attacks of malarial headache was their intolerance to physical exertion and exposure to the sun. This almost invariably brought about a severe headache. These men did not obtain relief with the usual remedies for headache. Salicylates, barbiturates, and even codeine, were found to be of no value in relieving this type of headache. On the assumption that the headache was the result of clogging of cerebral capillaries with parasite-laden red blood cells, with resulting venular congestion and cerebral anoxia, I tried using a vasodilating drug and found that the headache of many of these patients was relieved with 100 mg. of nicotinic acid taken orally.

I should like to ask Dr. Boshes how long the soldiers observed with cerebral manifestations had been in combat and what was the incidence of combat or operational fatigue in the entire series.

DR. CULLEN WARD IRISH, Los Angeles: Reports of cerebral malaria with localized manifestations have been few. Dr. Boshes' presentation adds to previous meager descriptions of such instances, of which there is a sufficient number, however, to emphasize the fact that cerebral malaria may assume any known form of disease of the nervous system.

I had the opportunity of observing a patient, a soldier aged 21, with residual symptoms of cerebellar involvement following malarial infection. This patient was in apparent good health until mid-January 1944, when he was admitted to

an Army hospital in the South Pacific. He was stuporous the first two days, but after treatment with quinine and quinacrine he recovered progressively and was discharged to duty Feb. 15, 1944. He then became increasingly weak, had much difficulty in standing and walking and suffered from persistent headache. After three days on duty he is said to have collapsed and was rehospitalized. The next day the gait was broad based and lurching, with flail-like movements of the legs, hyperreflexia and choking of the right optic disk.

On his transfer to the Army general hospital in this country, neurologic examinations revealed a broad-based, ataxic gait with gross tremors of both legs, so that the gait had a dancing quality. The patient fell to the left and backward in the Romberg position. No speech disturbance was present, but fine movements were impaired in both hands. A slight intention tremor occurred in coordination tests with the upper extremities, and there were severe tremor and ataxia in the lower extremities. Little improvement or change occurred.

In this case, it is apparent that the patient had acute cerebral involvement, manifested chiefly by stupor at the onset. A month later progressive weakness and tremor, particularly of the incoordination type, with persistent headache indicated the recurrence of intracranial malarial involvement. The caloric tests indicated that permanent damage had occurred in the pathways for equilibration. The rest of the symptoms were localizable to the cerebellum, where irreversible degeneration from foci of encephalomalacia had occurred.

Knowledge of such complications of malaria must be more widely disseminated. Recognition of the possibility that cerebral symptoms may be due to malaria, irrespective of knowledge of such exposure or of the region in which the patient may present himself, may be invaluable in saving life, since early proper therapeutics is commonly effectual.

DR. BENJAMIN BOSHES, Chicago: I am much interested in Dr. Hammon's concept that previous infection, such as virus infection, may break down the barrier and permit the plasmodium to break through and establish itself in the central nervous system. Symptoms may be divided into two types: meningeal symptoms and symptoms due to direct involvement of the blood vessels. I can conceive how a previous virus infection might break down the meningeal component of the barrier, with the result that the cerebrospinal fluid would show evidence of invasion. However, it appears to me that in our case the symptoms were due to vascular involvement, since the course of the localization, the jacksonian fits and the homonymous hemianopsia indicated that branches of the middle cerebral artery were involved. I might admit that when I first examined this patient my thinking was that of a civilian. I thought of virus infection and sent cerebrospinal fluid to the Army virus laboratory in Washington, D. C. I drew four samples of fluid, taking them in the afebrile and the febrile period. Admittedly, not many viruses can be identified specifically; however, all virus neutralization tests gave negative results.

The role of effort in relapses is important. Patients with hepatitis have prompt relapse on effort, and such patients were being returned to us as "psycho-neurotic." We learned to give them an exercise tolerance test and put them through an obstacle course before sending them back to combat. The same was true with "malarial" patients. We learned to put them through exercise and obstacle course and found that occasionally a patient with true malaria would have a relapse as soon as the soldier became active. I do not think that physical

exertion played an active role in the present case, that of a sergeant in the ground forces of the air corps.

We saw more cases of malaria and "malarial neurasthenia" among foot soldiers. I think this is related to the more frequent exposure of foot soldiers to malaria in the marshes of Sicily and Italy.

The intolerance of heat brings up an important point. An Italian physician in Naples told me that the Italian army had had no malaria during the Ethiopian campaign, but that there had been many cases of "heat stroke." I finally pinned him down to what he meant by "heat stroke." He admitted that there was so much malaria in the Italian army during the Abyssinian campaign and among the troops in Eritrea and elsewhere that Mussolini issued an edict that no diagnosis of malaria be made; henceforth, it should be called "heat stroke."

ORIGIN OF TUMORS OF THE MIDBRAIN

J. M. FRIEDMAN, M.D.*

NEW YORK

AND

L. GREENSTEIN, M.D.

BROOKLYN

ALTHOUGH tumors of the midbrain have been repeatedly described, the emphasis has invariably been placed on the clinical manifestations of such lesions. The tumors already recorded include many forms: A large number were in the nature of pineal growths; others had their origin in adjacent areas of the brain and only by contiguity and direct extension involved the midbrain. Globus and Silbert¹ clarified the histologic characteristics of a large quota of tumors of the midbrain of a somewhat varied appearance by identifying them as pinealomas, establishing this unity on an embryologic basis. They set these neoplasms apart from other neuroectodermal tumors occurring in that region. Such tumors, with their primary site of origin in the midbrain, are few. Bailey and Cushing² encountered 18 in the brain stem (pons and midbrain) in a total of over 1,000 gliomas. None of these was classified or described. Tooth,³ in a review of 500 cases of cerebral tumor, found 26 in which the midbrain was involved; in 8 of these the diagnosis was verified at autopsy, 4 of the tumors being classified as gliomas, 1 as a sarcoma, 2 as tuberculomas and 1 as a cyst. Several other authors (Marburg and Ranzi,⁴ Olivecrona⁵ and Dowman and Smith⁶), reviewing large series of brain tumors, included no instances

*Isadore Abramson Memorial Fellow in Neuropathology.

From the Neuropathologic Division of the Laboratories of the Mount Sinai Hospital.

1. Globus, J. H., and Silbert, S.: Pinealomas, *Arch. Neurol. & Psychiat.* **25**:937 (May) 1931.

2. Bailey, P., and Cushing, H.: *Tumors of the Glioma Group on a Histogenic Basis with a Correlated Study of the Prognosis*, Philadelphia, J. B. Lippincott Company, 1926.

3. Tooth, H. H.: Some Observations on the Growth and Survival Period of Intracranial Tumors Based on the Records of Five Hundred Cases, with Special Reference to the Pathology of the Gliomata, *Brain* **35**:11, 1912.

4. Marburg, O., and Ranzi, E.: Zur Klinik und Therapie der Hirntumoren mit besonderer Berücksichtigung der Endresultate, *Arch. f. klin. Chir.* **116**:96, 1921.

5. Olivecrona, H.: *Die chirurgische Behandlung der Gehirntumoren: Eine klinische Studie*, Berlin, Julius Springer, 1927.

6. Dowman, C. E., and Smith, W. A.: Intracranial Tumors: A Review of One Hundred Verified Cases, *Tr. South. S. A.* **40**:308, 1927.

of tumor of the midbrain. In a survey of cerebral tumors collected over a period of twenty years in the neuropathologic laboratory of the Mount Sinai Hospital, only 3 neoplasms were found to have had their true origin in the midbrain and confined to it. One of these was a hemangioma, and the other 2, to be reported here, were neuroectodermal tumors.

REPORT OF CASES

CASE 1.—History.—J. R., a man aged 29, ten days before admission to the Mount Sinai Hospital was suddenly seized with chills and severe pain in the left side of the back of his head. Stiffness of the neck followed, and five days later urinary incontinence developed. The next day he became delirious and soon



Fig. 1 (case 1).—Cross section of the midbrain, showing tumor within the aqueduct of Sylvius.

lapsed into a drowsy, dull state. During the following three days he was restless and unable to sleep. On the ninth day of his illness he passed through several generalized convulsive seizures with a short period of unconsciousness, followed by repeated vomiting. Throughout his illness there was no elevation of temperature.

Examination.—The patient appeared acutely ill and irrational, with slow, thick speech. The pupils were miotic, irregular and fixed to light and in accommodation. There were paralysis of convergence, fine nystagmoid twitchings on lateral fixation and slight skew deviation of the eyes. The eyelids showed bilateral ptosis. There were general muscular weakness, with hyperactive deep reflexes, and stiffness of the neck; a Kernig sign of moderate intensity and a Babinski sign were present bilaterally. Lumbar puncture yielded clear cerebrospinal fluid under an initial pressure of 168 mm. of water. The fluid contained 3 cells per cubic millimeter, and the Pandy reaction was negative.

Course of Illness.—Acute epidemic encephalitis was considered as the probable diagnosis. The patient's condition grew worse; he became stuporous and died on the ninth day in the hospital.

Gross Necropsy Observations.—There was moderate congestion of the vessels of the cortex. In retracting the frontal lobes, numerous adhesions were noticed in the perichiasmatic region. The floor of the third ventricle was greatly thinned and translucent, as a result of the internal hydrocephalus. The optic tracts appeared to be displaced laterally by the bulging of the tuber cinereum. A section through the midbrain displayed an obstruction in the aqueduct just caudal to the junction with the third ventricle. It appeared to have been caused by a small



Fig. 2 (case 1).—Section of the tumor, showing its relationship to the subependymal cell plate in the floor of the aqueduct.

round body containing two or three yellowish cystic areas (fig. 1). The aqueduct was greatly dilated rostrad to the obstruction and slightly dilated below it. At the point of obstruction it seemed to be completely obliterated, and its site marked an area of yellowish discoloration outlining approximately the extent of the periventricular gray matter. Viewed from the caudal aspect, the free and rounded surface of the tumor projected freely into the anterior part of the fourth ventricle. The ventricular system rostrad to the aqueduct was considerably enlarged, the internal hydrocephalus being symmetric. The interventricular foramina were large and provided a wide intercommunication between the two lateral ventricles, as well as with each other.

Microscopic Observations.—The tumor tissue, sections of which were stained with hematoxylin and eosin, was densely cellular and moderately well vascularized. There were encountered a few large cystlike spaces, surrounded by somewhat loose tissue. Within these spaces were compound granular cells. On tracing the periphery of the tumor mass one found that the growth was intimately related to the subependymal tissue, suggesting the probability that the neoplasm was an outgrowth of the subependymal cell plate in the region of the floor of the aqueduct, reducing the aqueduct to a narrow slit (fig. 2). Except for bare areas and the site of fusion with the tumor, the aqueduct retained a fairly normal ependymal lining. Uninterrupted ependyma extended also over a portion of the protruding tumor mass. In one segment the ependymal lining was thickened and displayed several cell layers, which gradually blended with the neoplastic tissue (fig. 3). At

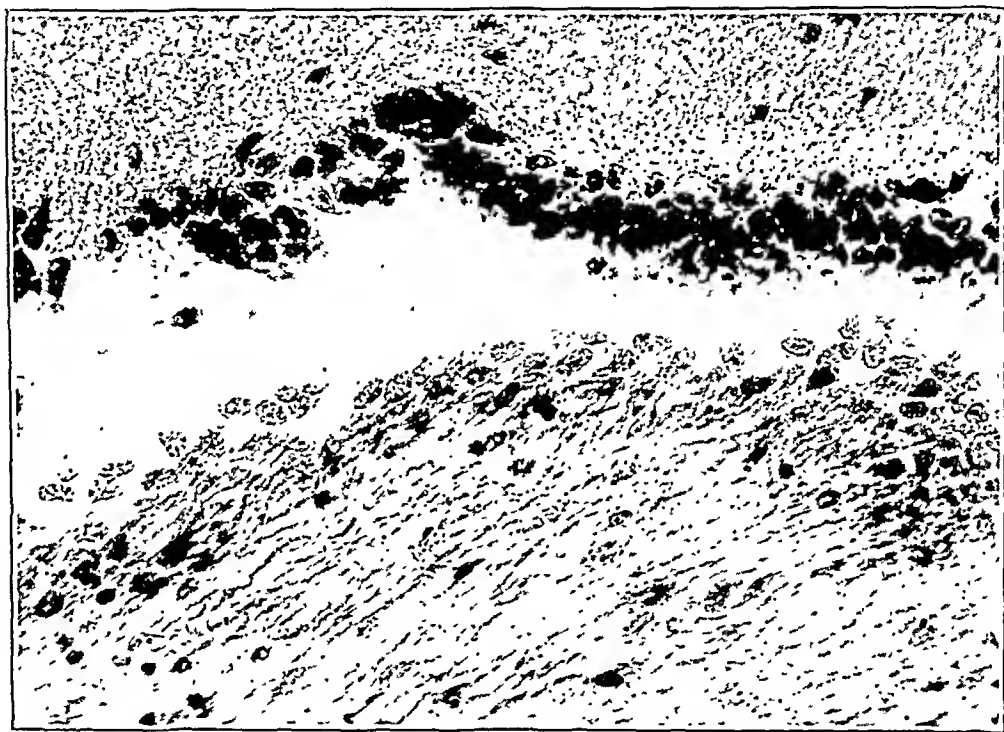


Fig. 3 (case 1).—Section of the tissue, showing stratified ependymal epithelium lining the surface of the tumor and the aqueduct.

points of contact of the tumor with the wall of the aqueduct ependymal lining separated it from the uninvolved brain tissue (fig. 4).

The dominant cell in the tumor was a long, fusiform bipolar cell, giving rise to rather long fibrous extensions. These fibers were arranged in broad, streaming bundles, running in various directions. In addition, there were stellate glial elements, which showed several transitional stages toward the elongated, spindle-shaped type. In some segregated areas there were multinuclear, but rather moderate-sized, cells of the spongioblastic giant cell variety. A few large neuroblasts were scattered among the other tumor cells, as were a few mitotic figures.

Many of the vessels showed perivascular infiltration with small round cells. Silver preparations revealed a network of fine argentophil fibers within the tumor. These fibers were directly continuous with the adventitial reticular framework of the blood vessels. The gray substance of the tegmentum in the proximity of the tumor contained degenerating nerve cells, showing the picture of tigrolysis.

Among the cells of the oculomotor nucleus was an occasional binucleated motor cell (fig. 5).

In serial cross sections of the tumor stained with hematoxylin and eosin, remnants of ependymal cysts were seen in the depths of the basal plate of the aqueduct (fig. 6).

Comment.—This tumor presented a significant feature in its topographic relation to the subependymal cell plate surrounding the aqueduct. The tumor gave the impression of being well demarcated from the surrounding tissue, thus showing an expansive, compressing type of growth rather than an infiltrating, invasive one. The expansion was directed toward the aqueductal space. At its base the tumor extended nowhere

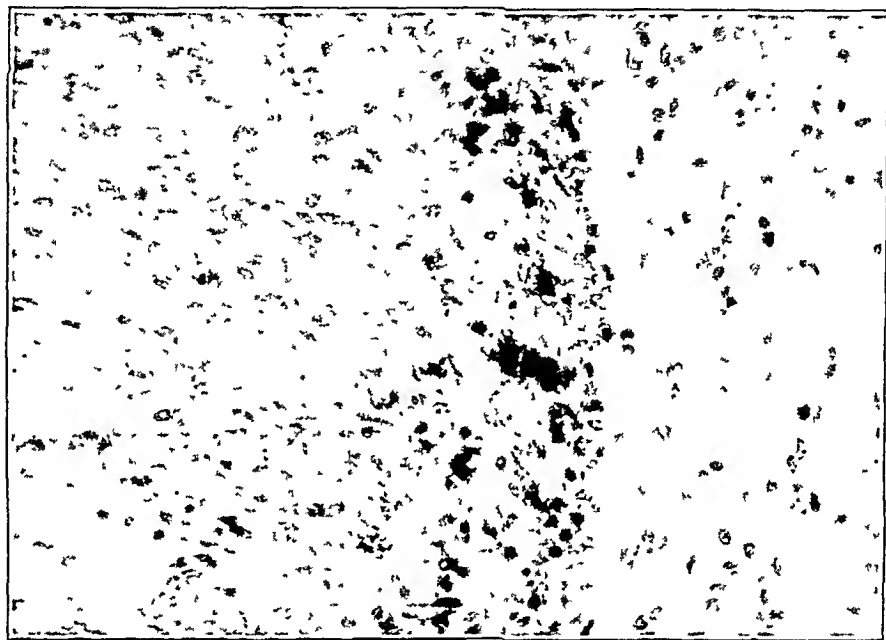


Fig. 4 (case 1).—Section of the tumor, showing a band of cells marking the separation between tumor tissue and the adjacent, apparently unaltered, part of the brain stem.

beyond the limits of subependymal cell plate. In this zone the neoplastic cells gradually blended through transitional cell forms with the normal elements of the subependymal cell plate. The topographic relations of this tumor and certain constant embryonic changes observed by Turkewitsch⁷ and Hochstetter⁸ in the developing aqueduct point to a probable source of this primary tumor of the midbrain.

In the course of an extensive search, suggested by Dr. Globus, for the probable embryonic factors bearing on the development of primary

7. Turkewitsch, N.: Die Entwicklung des Aqueductus cerebri des Menschen, *Morphol. Jahrb.* 76:421, 1935.

8. Hochstetter, F.: Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns, Vienna, Franz Deuticke, 1919, pt. 2.

neoplasms of the midbrain, there were encountered the highly significant and suggestive observations of Turkewitsch⁷ and Hochstetter.⁸ In median longitudinal sections of the midbrain of human fetuses of from 4 to 8 months, Turkewitsch observed ependymal folds covering the surface of the tegmental colliculi and projecting into the passage of the midbrain (fig. 7). In their ultimate obliteration by fusion, ependymal



Fig. 5 (case 1).—Section of the tumor, showing a vessel infiltrated with dark-staining cellular elements and streaming fusiform cells.

residues were often observed to persist. Hochstetter, on the other hand, in cross sections of human embryos of 3 months, observed symmetrically located areas denuded of ependymal epithelium at the junction of the caudal sac of the midbrain with the cavity of the midbrain. The bare surfaces were covered by a large number of round cells, and in the exposed matrix there were usually encountered subependymal cell groups.

The persistence of embryonic elements in the basal plate of the aqueduct at its junction with the caudal sac of the midbrain, as observed by Turkewitsch, is significant, as these residual nests constitute a



Fig. 6 (case 1).—*A*, serial section of tumor, showing ependymal cyst at the periphery of the tumor (in the rectangle). *B*, higher magnification of the ependymal cyst.

by-product of an excessive growth of ependymal folds which normally undergo complete involution and serve as a nucleus of neoplastic forma-

tion. The persistence of the bare areas in the developing aqueduct, as observed by Hochstetter, is significant in that, the restraining influence of a limiting membrane being absent, any blastomatous formation arising

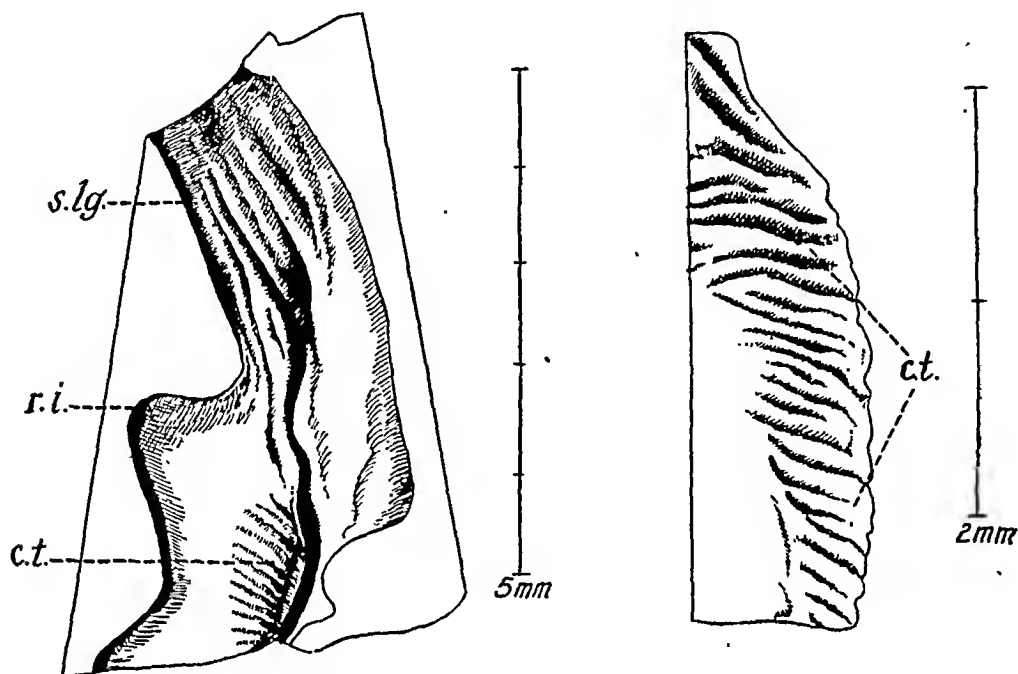


Fig. 7.—Drawing, after Turkewitsch⁷ illustrating the aqueductal channel in the fetus and showing the folds over the colliculus tegmenti (*c.t.*); the other landmarks are the recessus isthmi (*r.i.*) and the sulcus longitudinalis (*s.lg.*).

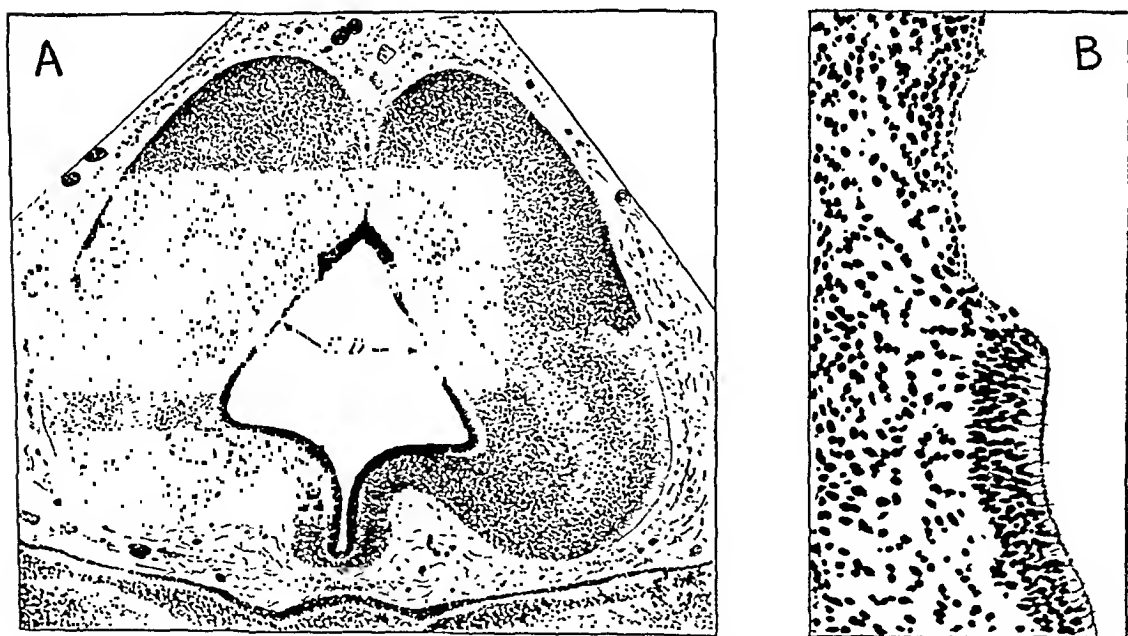


Fig. 8.—*A*, drawings, after Hochstetter,⁸ illustrating the site in the midbrain sac in which the ependymal lining is missing (*E.D.*). *B*, the denuded area, shown in *A* (*E.D.*), under higher magnification.

ing from the embryonic elements in the basal plate of the aqueduct would tend to be directed in its growth into the aqueduct.

CASE 2.—*History*.—I. R., a man aged 56, entered the Mount Sinai Hospital on Aug. 24, 1928. He had been in good health until three months before admission, when he began to complain of intermittent headaches recurring nightly,



Fig. 9 (case 2).—*A*, section of tumor, showing the structure of a spongioblastoma multiforme. *B*, ependymal lining covering the tumor, with pseudostratified ependyma covering the normal tissue.

accompanied with dizziness, which persisted during the following day. His headaches gradually increased in severity and duration. Nine days prior to his admission it was noted that he was unable to turn his eyes to the left, and the

left side of his face became distorted and numb. Difficulty in swallowing appeared, and weakness developed in both lower extremities. A few days later he complained of double vision.

Examination.—The pupils were irregular and unequal, the left being larger than the right. Both pupils reacted poorly to light and in accommodation. The fundi showed extremely tortuous vessels, with slight blurring of the disk of the left eye. Both eyes were in conjugate deviation to the right. On his looking to the left, the right eyeball could be brought almost to the midposition, but the left eye remained deviated to the right. His voice was hoarse, and swallowing was difficult. There was a supranuclear paralysis of the left facial nerve. The pharyngeal reflex was greatly diminished. Hemiparesis with increased deep reflexes and a positive Babinski sign was present on the left side. Sensory examination showed diminished vibratory perception in the left lower extremity up to the iliac crest. Gait was ataxic, and there was a tendency to fall to the left. The blood pressure was 160 systolic and 110 diastolic. Lumbar puncture yielded clear cerebrospinal fluid. The Wassermann reactions of the blood and cerebrospinal fluid were negative, and the colloidal gold curve was normal.

Course of Illness.—There was rapid development of signs and symptoms. Paralysis of upward gaze, as well as lateral conjugate deviation of the eyes, appeared, with preservation of convergence. Speech became bulbar, and there developed paralysis of the left recurrent laryngeal nerve and hemihypalgnesia and thermhypesthesia on the right side. Because of the rapid clinical course, a progressive intrapontile vascular thrombosis was suspected. His general condition became poor, and he died on Sept. 5, eleven days after admission.

Gross Necropsy Observations.—Section of the brain revealed a tumor, measuring about 3 cm. in diameter, in the midbrain. The growth involved the left cerebral peduncle in its entire length, extending dorsally into and displacing the tegmentum. The tumor extended caudally a short distance into the pons.

Microscopic Observations.—The tumor tissue was richly vascular and highly cellular. The cells contained deeply staining nuclei and were arranged in streams, whorls and rosettes, many without any definite pattern (fig. 9). The cell bodies were poorly defined. They were irregular in shape and stained poorly. Scattered among them were numerous giant cells, many of which were pyriform and contained several nuclei. The capillary walls were thickened, had a structureless, homogeneous appearance and were infiltrated with tumor cells. Within the tumor and the adjacent tissue were necrotic areas filled with debris and compound granular cells. These areas were surrounded by several layers of tumor cells in rosette formation. A segment of the tumor tissue was covered by normal ependyma. Pseudostratified ependymal epithelium covered the surface of a segment of normal tissue.

Comment.—Although the tumor in this case differed in its site of origin from that in the first case, both probably have embryonic residues as their source of origin. Two morphologic features, as Hochstetter emphasized in his observations on the midbrain, are responsible for the narrowing of the cavity of the embryonic midbrain, namely, the addition of fiber tracts and the proliferation and early migration of subependymal cells. Some of these cells become arrested in their migration, retain their embryonic proliferative potentialities and form centers of incompletely differentiated neuroectodermal elements. The source

of the second tumor is probably to be found in these heterotopic elements.

SUMMARY

Two cases of primary neuroectodermal tumors which had their primary site in the midbrain are described.

An attempt is made to correlate their source of origin with embryonic alterations in the developing midbrain.

Persistence of ependymal and subependymal cells, constituting a by-product of an excessive growth of ependymal folds which must undergo complete involution and obliteration, is considered the source of the tumor (transitional glioma) in the first case.

Persistence of migrated potent subependymal cells, forming centers of growth at a distance from the subependymal zone (heterotopias), suggests the origin of the tumor (spongioblastoma multiforme) in the second case.

The migration of subependymal cells represents an earlier phase in the development of the midbrain than the formation of subependymal folds. Therefore it is probable that the tumor arising from heterotopic elements is made up of less differentiated cell types than one arising from embryonic structures which make their appearance later in prenatal development.

TOXIC EFFECTS OF INTRATHECAL ADMINISTRATION OF PENICILLIN

A. EARL WALKER, M.D.

CHICAGO

PENICILLIN has been regarded as quite harmless even when administered in large doses and it is true that toxic manifestations are relatively rare as a result of parenteral administration. This is not the case when the drug is administered intrathecally, particularly if the dose is excessive. To illustrate this fact, which has not been generally recognized, two types of complications following intrathecal administration of penicillin are presented.

EXPERIMENTAL BASIS

In a series of experiments on the macaque monkey, on thirteen occasions 20,000 units of penicillin in 1 cc. of isotonic solution of sodium chloride was injected intrathecally. Within ten to fifteen minutes the animals were observed to look at, rub and then vigorously scratch their tails and perianal regions. This behavior persisted for at least an hour in some instances. In the monkey, these paresthesias appeared to be temporary, for the animal was well the following morning. The spinal cords of 5 macaque monkeys which had been given intrathecal injections of penicillin were examined. Although none of these monkeys showed clinical evidence of neural involvement at the time they were killed, 3 of the 5 spinal cords showed histologic alterations.

Sections from the lumbar portions of the spinal cord and the cauda equina were stained by Nissl's method, with hematoxylin and eosin with Perdrau's technic for reticulin and for myelin. In the cauda equina of 3 animals a patchy demyelination was present in the nerve roots. In these areas proliferation of the sheath cells was apparent. Between the roots of the cauda equina was a delicate proliferation of the arachnoid, binding together the roots of the cauda equina. Only an occasional lymphocyte was seen in the meshes of the arachnoid. The dura mater showed no alteration. The parenchyma of the spinal cord appeared relatively normal except for tigrolysis of an occasional anterior horn cell.

This work was carried out while Dr. Walker was assigned to the Cushing General Hospital, Framingham, Mass.

CLINICAL EVIDENCE OF TOXICITY OF THE DRUG

That similar radicular reactions may occur after the intrathecal injection of penicillin in man has previously been noted by a number of authors. Following the treatment of purulent meningitis by intrathecal injection of penicillin, Sweet, Dumoff-Stanley, Dowling and Lepper¹ noted that several of their patients exhibited disturbances of the bladder and paresthesias and weakness of the lower extremities. Walker and Johnson² reported a case of sacral radiculitis following the intrathecal administration of penicillin for a meningeal reaction secondary to a cholesteatoma of the mastoid. Their patient had urinary retention and severe motor and sensory disturbances in the legs. The dysuria cleared up rather quickly, but the other disturbances persisted for four months. As an illustration of this type of complication, the following case is presented.

REPORT OF CASES

CASE 1.—On Aug. 8, 1945, a soldier aged 32 fell from a second story window, sustaining a laceration over the right eye. The following day his temperature

TABLE 1 (case 1).—*Laboratory Findings and Results of Penicillin Therapy*

Date	Highest Temperature	Spinal Fluid			Penicillin, Units		Comment
		Cells per Cu. Mm.	Poly-morpho-nuclears, %	Lym-pho-cytes, %	Intra-the-cally	Intra-venously	
Aug. 10	40 C. (104 F.)	7,100	96	4	40,000	Pneumococcus in cerebrospinal fluid
11	40	6,850	11	89	40,000	400,000	89% lymphocytes; culture sterile; voided
12	20,000	350,000	800 cc. by catheterization; spinal tap unsuccessful
13	320,000	Spinal tap unsuccessful
14	..	1 cc. only	200	..	40,000	320,000	
15	320,000	
16	360,000	Patient catheterized
17	320,000	
18	320,000	
19	240,000	
20	..	20	320,000	
Aug. 21 to Sept. 10	240,000	Sulfadiazine, 1 Gm./4 hr.
Sept. 10 to 21	120,000	Sulfadiazine, 1 Gm./8 hr.

was 100.4 F. A spinal puncture yielded a cloudy fluid, containing pneumococci on culture. The patient was given 40,000 units of penicillin intrathecally on the second, third and sixth days of his illness and 20,000 units intrathecally on the

1. Sweet, L. K.; Dumoff-Stanley, E.; Dowling, H. F., and Lepper, M. H.: The Treatment of Pneumococcic Meningitis with Penicillin, *J. A. M. A.* **127**:263-267 (Feb. 3) 1945.

2. Walker, A. E., and Johnson, H. C.: Principles and Practice of Penicillin Therapy in Diseases of the Nervous System, *Ann. Surg.* **122**:1125-1135, 1945; Penicillin in Neurology, Springfield, Ill., Charles C Thomas, Publisher, 1946.

fourth day (table 1). Shortly after the first intrathecal injection of penicillin he had difficulty in voiding and required catheterization. He recovered completely from the meningitis, but his urinary disturbances persisted. For five months after his meningitis the patient complained of pain about the left ankle and constipation. Examination revealed perianal hypesthesia and a severely atonic rectal sphincter. The knee jerks were equal and active. The ankle jerks were sluggish. Flexion of both knees and of the left foot was weak. The patient tired after walking one block. Examination of his spinal fluid four months after the meningitis revealed no abnormality.

The disturbances may be even more severe than those illustrated by case 1. An intense arachnoiditis associated with myelitis has been reported in a number of cases, and many more such instances have occurred which have not yet been recorded in the literature. Forrest³ reported a case in which transitory pain and weakness developed in the upper extremities after the use of penicillin for meningococcic meningitis. Siegal⁴ reported a case of transverse myelopathy following recovery from pneumococcic meningitis treated with penicillin intrathecally. Bailey⁵ mentioned a case in which intrathecal administration of penicillin was followed by paraplegia and at a subsequent operation a marked leptomeningeal thickening was observed. It is true that Bailey ascribed the meningeal reaction not to the use of the drug but, rather, to the disease process. While it is impossible to state with certainty that the primary disease was not responsible for the complication, the fact that myelitis is a rare sequel of meningitis treated with sulfonamide drugs⁶ and other agents⁷ indicates that some other factor was responsible. After penicillin therapy for meningitis, especially if large amounts of the drug have been used, myelitis is not infrequent. A case is presented in detail to illustrate this complication.

CASE 2.—A married man aged 33 was admitted to Cushing General Hospital Dec. 17, 1945, because of paralysis of both legs, decubitus ulcers over the sacrum and hips and convulsive seizures. The patient was struck by shell fragments on Nov. 14, 1944, while digging a foxhole, sustaining wounds in the right frontoparietal region and the right supraclavicular region. He was not rendered unconscious and was able to walk to the field hospital, where his wounds were debrided. However, his left leg became weak, and on November 19 both the left arm and the left leg were paralyzed. The hemiplegia began to improve and two weeks

3. Forrest, A. R.: Neurological Complications in Cerebrospinal Meningitis Treated with Penicillin, *Brit. M. J.* **2**:805-806, 1945.

4. Siegal, S.: Transverse Myelopathy Following Recovery from Pneumococcic Meningitis Treated with Penicillin Intrathecally: Report of Case, with Note on Current Methods of Therapy, *J. A. M. A.* **129**:547-550 (Oct. 20) 1945.

5. Bailey, P.: Chronic Leptomeningeal Thickening Following Treatment of Meningitis with Sulfa Drugs, *Ann. Surg.* **222**:917-922, 1945.

6. Farmer, T. W.: Neurologic Complications During Meningococcic Meningitis Treated with Sulfonamide Drugs, *Arch. Int. Med.* **76**:201-209 (Oct.) 1945.

7. Degen, J. A.; Cameron, H.; Robinson, V. L. M., and Wieden, M. S. R.: Sequelae of Cerebrospinal Meningitis, *Brit. M. J.* **2**:243-247, 1945.

later was mild. On December 5 with procaine anesthesia, an abscess of the right frontoparietal region was evacuated, and fragments of bone were removed from the cavity. Because of cerebral herniation, a spinal puncture was performed and 25,000 units of penicillin instilled into the subarachnoid space. The cultures of the spinal fluid were sterile. Cultures of material from the wound yielded a nonhemolytic streptococcus. Approximately twelve hours later another spinal puncture was made. The fluid was said to be normal, but 15 cc. was removed and 50,000 units of penicillin in 10 cc. of isotonic solution of sodium chloride was instilled into the intrathecal space. The patient was also given 25,000 units of penicillin every four hours intramuscularly and 1 Gm. of sulfadiazine every four hours. On December 6 it was noted that both legs and the left arm were very weak and the patient was unable to void. A spinal puncture was performed, the initial pressure being 400 mm. of spinal fluid. After removal of fluid, 50,000 units of penicillin was injected intrathecally (table 2). On December 7 both legs were completely paralyzed. The next day, although the patient was mentally

TABLE 2 (case 2).—*Data on Clinical Course, Laboratory Study and Intrathecal Penicillin Therapy*

Date	Highest Temperature, C.	Spinal Fluid		Penicillin (Intrathecal), Units	Comment
		Cells	Cultures		
Nov. 14	Date of injury; primary débridement
19	Left hemiparesis
Dec. 2	Hemiparesis almost gone
5	"Normal"	25,000	Secondary débridement; drainage of abscess
6	37.8 (100 F.)	Sterile	50,000	Unable to void; legs weak
7	38 (100.4 F.)	Sterile	Both legs paralyzed
8	38	
9	0	Sterile	Left arm improving

clear, the paralysis of the legs remained unchanged. On December 14 the left arm could be moved but the legs remained paralyzed. No note was made regarding reflex or sensory disturbances until Jan. 5, 1945, when it was recorded that the reflexes of the lower extremities were absent and that there was sensory loss over the lower part of the body and legs.

On Jan. 22, 1945, the patient, on admission to O'Reilly General Hospital, had complete flaccid paraplegia, areflexia of the lower extremities and anesthesia below the level of the fourth thoracic dermatome. The tendon reflexes of the left upper extremity were more active than those on the right. On June 27, 1945, a tantalum cranioplasty was performed. Because of two convulsive attacks, the patient was transferred to Cushing General Hospital on Dec. 17, 1945.

At the time of his admission he was well nourished, but his skin was yellow from quinacrine (atabrine), although the scleras were clear. He had flaccid paralysis of both legs with absence of superficial and deep reflexes. The upper and middle abdominal reflexes were present on the right side. The abdominal reflexes were absent on the left side. The tendon reflexes of the left upper extremity were more active than those of the right, and there was a questionable Hoffmann sign in the left hand. Healed wounds were present in the right supraclavicular area and the right temporoparietal region of the scalp. No scar was present over the cervical portion of the spine. A urethral catheter was kept in place for tidal drainage of the bladder. The spleen was palpable approximately

3 cm. below the costal margin and the liver barely palpable. There was a large decubitus ulcer over the sacrococcygeal region, extending almost to the anus. The base was covered by fairly clean granulation tissue except for the upper part, which had a skin graft. Over each greater trochanter was an ulcer 3 cm. in diameter. On Jan. 30, 1946, the ulcers over the trochanters were closed by rotation flaps. The wound on the left side broke down because of formation of a hematoma, and a secondary closure was made on Feb. 15, 1946; and at the same time a split thickness graft was placed over the granulating sacral ulcer. The wounds healed well after this procedure. On March 21, 2 cc. of "pantopaque"



Photograph of the operative field in case 2, showing the considerable leptomeningeal thickening. The dura mater is held open by silk sutures.

(an iodized poppyseed oil, with special cohesive properties) was injected into the cisterna magna and observed under the fluoroscope to flow freely to approximately the third cervical vertebra, where it seemed to stop. With lumbar puncture, 2 cc. of "pantopaque" was injected into the subarachnoid space at the fourth lumbar vertebra. Fluoroscopically, the medium was observed to flow to the interspace between the eighth and the ninth dorsal vertebra. It was then seen that the small amounts of the medium injected into the cervical region had reached the seventh cervical segment. The contrast medium was collected in small globules on either side of the spinal cord. Roentgenograms taken one week later showed

small drops of "pantopaque" scattered throughout the dorsal portion of the spinal canal with larger collections of the medium overlying the interspace between the twelfth dorsal and the first lumbar vertebra and that between the third and the fourth lumbar vertebra. There was a rather uniform distribution of the droplets throughout the dorsal region. Roentgenograms of the skull showed no evidence of the contrast medium in the intracranial cavity. It was thought that arachnoiditis would best explain the roentgenographic findings.

On March 27, 1946, with the use of procaine anesthesia, a laminectomy was performed. Along the site of the proposed incision in the midthoracic region, 1 per cent procaine hydrochloride was injected. The spinous processes from the fourth to the seventh thoracic vertebrae inclusive were then removed and their laminae rongeured away. The dura mater was then opened. It was observed to be strongly adherent to the underlying pia-arachnoid, and only with great difficulty were the two separated. The arachnoid was then seen to be 2 to 3 mm. thick, and it was difficult to detect the division between the arachnoid and the spinal cord. Near the upper third of the exposed area, a cyst, 1 cm. in length and 5 mm. in width, was observed, covered by greatly thickened arachnoid. On opening it, a small amount of spinal fluid was seen to pulsate with respiratory and cardiac activity. About this cyst was thickened arachnoid, and on its medial surface was what appeared to be a greatly sclerosed spinal cord (figure). A small piece of arachnoid was taken for biopsy. The dura mater was then closed, with strips of fibrin foam laid over the line of suture. The muscles were then approximated and the edges of the skin brought together with silk sutures. The patient had an uneventful convalescence from this procedure, and the wound healed by primary intention. His neurologic status remained unchanged.

Examination of the tissue removed at operation was reported by Capt. J. Churg as showing dense fibrous tissue in parallel layers with numerous small fibrocytic nuclei. Embedded in the tissue were small bundles of nerve fibers showing moderate edema and some degenerative changes. Occasional collections of small round cells were present.

COMMENT

It is known that intrathecal medication may produce leptomeningeal reactions, and many substances when injected into the subarachnoid space have been found to be responsible for such alterations in the arachnoid. That penicillin may give rise to the same result is not unexpected. Whether the primary effect of the drug is on the leptomeninges or the nerve tissue cannot be determined from this study. In view of the rapid onset of the reaction in some cases, it would seem probable that the nerve tissue was damaged early. On the other hand, the arachnoidal alterations appeared to precede the neural damage in the experimental neuropathy induced in monkeys by intrathecal injection of penicillin.

In the cases presented, and in most cases of similar complications reported in the literature, the amount of penicillin administered at one time was greater than is usually advised. Whether the concentration of the penicillin or the total amount given is the more potent factor in producing this complication is difficult to determine, for usually a large dose is associated with a high concentration of the drug. It would seem,

however, that intrathecal administration of penicillin in doses not in excess of 20,000 units and well diluted with the spinal fluid is unlikely to cause this complication.

There is no evidence that the use of very large amounts of penicillin is more effective in the treatment of purulent meningitis than the use of moderate doses, provided the penicillin is thoroughly distributed throughout the subarachnoid space. An adequate antibiotic level throughout the entire subarachnoid space can be obtained with the use of penicillin given into the cisterna magna or into the ventricle, thus eliminating the necessity of large doses in the lumbar region. Experimental studies on both animal and man have shown that the distribution of penicillin when so given is superior to that when the drug is administered in the lumbar region.

SUMMARY

Two cases illustrating types of neural reaction to intrathecal administration of penicillin—radiculitis and myelopathy associated with chronic leptomeningeal thickening—are presented. Such reactions usually occur only when large amounts of penicillin are injected into the subarachnoid space. When moderate or small doses of the drug are used, the complication is rarely encountered.

950 East Fifty-Ninth Street, Chicago (37).

DYSTONIC FORM OF AMAUROTIC FAMILY IDIOCY

Report of a Case

ALUIZIO MARQUES, M.D.
RIO DE JANEIRO, BRAZIL

AMAUROTIC family idiocy has rarely been described in Brazilian literature. The infantile form of the disease was studied and described by Julião, Magalhães and Brandi. Marques¹ (1943) reviewed the subject and presented a case characterized by amaurosis, atrophy of the optic nerve, pigmentary retinosis, muscular hypotonia, convulsions, mental regression and the added stigma of spina bifida. The purpose of this paper is to present a case of amaurotic family idiocy in which diagnosis was possible only after careful histologic study.

REPORT OF CASE

The patient was first seen in the neurologic clinic of the Getulio Vargas Hospital at the age of 17 years. After preliminary examination, he was admitted to the hospital, with well defined signs of a dystonic syndrome, characterized by slow and spasmodic twitching of the face, spasmodic twitching of the trunk and neck and slow and spasmodic hyperkinetic movements of both the upper and the lower extremities.

The family history revealed that the patient's mother and father were living and well and were not blood relatives. The family antecedents were Brazilians of Portuguese extraction, not of Jewish origin. There was no history suggestive of neurologic disease in any member of the family except for 1 sibling, aged 9, who for the past two years had had neurologic signs similar to those presented by the patient.

The birth of the patient had been normal, no forceps being used. The weight at birth was 7 pounds 8 ounces (3,400 Gm.). He had had no serious disease or operation. He was said to have grown and developed well up to 9 years of age. At the time of examination he was 4 feet 11 inches (149 cm.) in height and weighed 106 pounds (48.1 Kg.). There were no bodily deformities; the face presented twitchings. Examination of the heart, lungs and abdomen revealed nothing abnormal. The pulse rate was 80 and the blood pressure 110 systolic and 60 diastolic. The blood and the cerebrospinal fluid gave negative reactions for syphilis.

The parents dated the onset of the illness to the age of 9 years. Prior to that time the child had been entirely normal, physically and mentally, and he was progressing well in school. At the age of 9, dysarthria and a mild intention tremor developed, and progressive mental deterioration was noted. No visual disturbances

From the Neurological Clinic of the Getulio Vargas Hospital.

1. Marques, A.: *Idiotia amaurótica familiar: Estudo de um caso pessoal e revisão da casuística brasileira*, Arq. neuro-psiquiat., São Paulo 1:207-233 (Dec.) 1943.

occurred. Gradually progressive, slight dystonia was noted through the years by the parents, whose story may be regarded as only fairly reliable. This dystonia eventually progressed to hypertonia and hyperkinesia, and profound dementia developed.

Physical examination revealed a well developed, well nourished white youth. The outstanding features on inspection were a slow, spasmodic twitching of the face, trunk and neck; hyperkinesia of the upper and lower extremities, and extreme voluntary hypermotility (fig. 1 *A*). Gross inspection revealed abnormally large feet, with the characteristic hollowing observed in status dysraphicus (fig. 2).



Fig. 1.—Cinematographic reproductions of a patient 17 years of age, showing (*A*) athetosis of the lower extremities and tonic distortion of the trunk and neck and (*B*) movements of the face.

The patient presented no ocular disturbances, nor was there paralysis of the muscles of the eyeball, either external or internal. The photomotor reflex was normal. Examination of the fundus showed that the retina, optic disk, veins and arteries were normal.

The clinical impression was that of hepatolenticular degeneration (Wilson's disease) or Hallervorden-Spatz disease.

The patient died four months after entering the hospital. The clinical picture remained unchanged from the date of admission, but, as he ate little and had diarrhea, he suffered gradual starvation and marasmus and finally died in a state of cachexia.

Histologic examination of the retina showed nothing abnormal. The optic disk and the optic nerve were normal.

Macroscopic and microscopic examination of the viscera (heart, lungs, liver, spleen, kidneys and digestive organs) revealed nothing significant except for slight atrophy of the heart muscle and slight signs of degeneration of the liver, changes

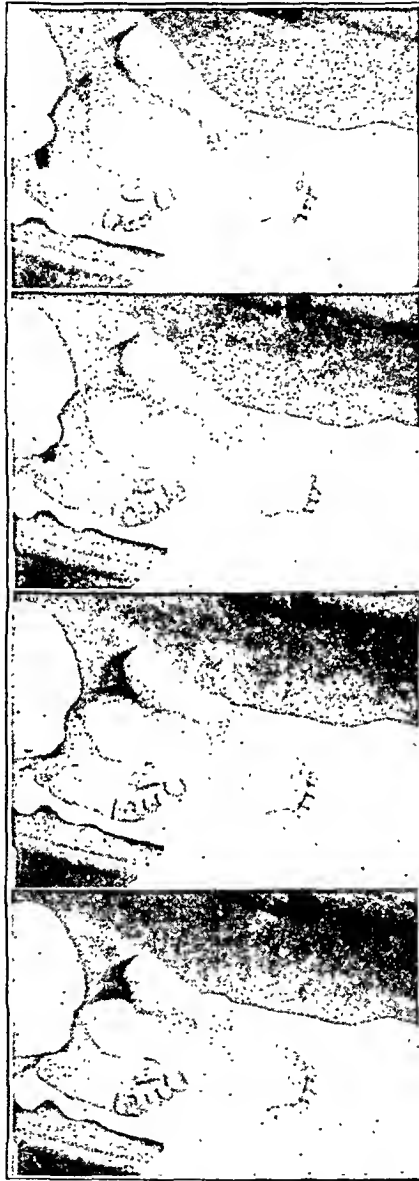


Fig. 2.—Hollow plantar arch and distorted toes, produced by the athetosis constantly shown by a patient with amaurotic family idiocy, dystonic form.

which might be attributed to the state of cachexia that preceded death. In the intestine, especially the colon, there were signs of inflammation, referable to the enteritis which manifested itself during the latter part of the patient's life.

Histologic study of the liver and brain ruled out a consideration of hepatolenticular degeneration. Further histologic study (W. E. Mafei) led to the belief that the patient presented a form of amaurotic family idiocy without ocular involvement.

Histologic examination revealed marked alteration of the nerve cells, including those of the cerebral cortex, basal ganglia, thalamus, cerebellum, pons, medulla and spinal cord. Only minor variations were noted in the intensity of the process in the different regions. The Nissl stain revealed that the cells were enlarged and balloon shaped, with the nucleus displaced to the periphery (fig. 3). The cytoplasm was delicate in appearance, but was occasionally spongy, containing large vacuoles. The chromophilic substance was dense and stained deeply near the nucleus but was otherwise sparse and did not take the stain well. The nuclei in general, except for their peripheral position, had a rather normal appearance and were only occasionally hyperchromic.

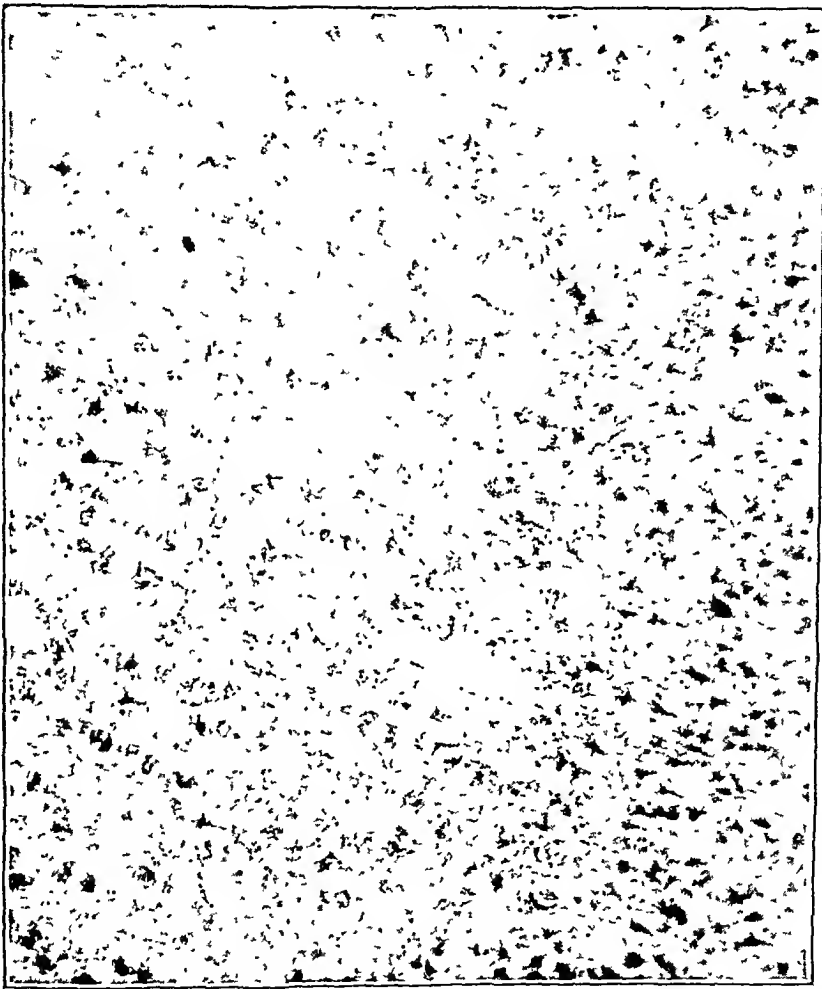


Fig. 3.—Section of the cerebral cortex of the frontal lobe of a patient with amaurotic family idiocy, showing the balloon-shaped cells. Nissl method; Leitz ocular 4; objective 5.

The Weil stain for myelin, as well as the Bielschowsky method, revealed nothing of interest in the white matter of the brain, nor were the neurofibrils abnormal. As previously mentioned, the outstanding characteristic was the wide distribution of the balloon-shaped cells, which gave very similar pathologic pictures in the cerebral cortex, the basal ganglia (fig. 4) and the substantia nigra.

The swollen area of the nerve cell contained granules which stained deep red with sudan III, suggestive of prelipid granulation and lipofuchsin. Around capillaries in the cerebral cortex and the basal ganglia the same pigment was seen. In addition, the capillaries showed calcification.

In sections stained with Weil's myelin technic, the predominance of the fibers in the globus pallidus presented a picture of status fibrosus. The Globus method for macroglia showed hyperplasia of the pyramidal cells in the third layer of the prefrontal area of the cerebral cortex (fig. 5). The balloon-shaped cells, with loose, delicate cytoplasm and peripheral nuclei (figs. 6 to 10), together with the changes revealed with special stains and the distribution of the pathologic factors pointed to a diagnosis of amaurotic family idiocy.



Fig. 4.—Section of the corpus striatum, showing the abundance of fibers. Weil method for myelin; Leitz microsumar lens, 8 mm.

COMMENT

A review of the literature on amaurotic family idiocy, including publications by Globus,² Hassin, Vogt, Spielmeyer,³ Josephy,⁴ Sjögren

2. Globus, J. H.: Amaurotic Family Idiocy, *J. Mt. Sinai Hosp.* **9**:451-503 (Nov.-Dec.) 1942.

3. Spielmeyer, H. W.: Zur Pathogenese örtlich elektiver Gehirnveränderungen, *Deutsche Ztschr. f. Nervenhe.* **89**:13-17, 1926.

4. Josephy, H.: Familiäre amaurotischen Idiotie, in Bumke, O., and Foerster, O.: *Handbuch der Neurologie*, Berlin, Julius Springer, 1936.

and Sjövall, revealed no case in which the picture was similar to that in the one described here. The literature shows no case of amaurotic family idiocy presenting the extrapyramidal syndrome described in this case. The hypokinetic and akinetic symptom complex described by Sjögren and Sjövall, while having a possible extra pyramidal origin, in no way resembles the dystonic form described in this case.

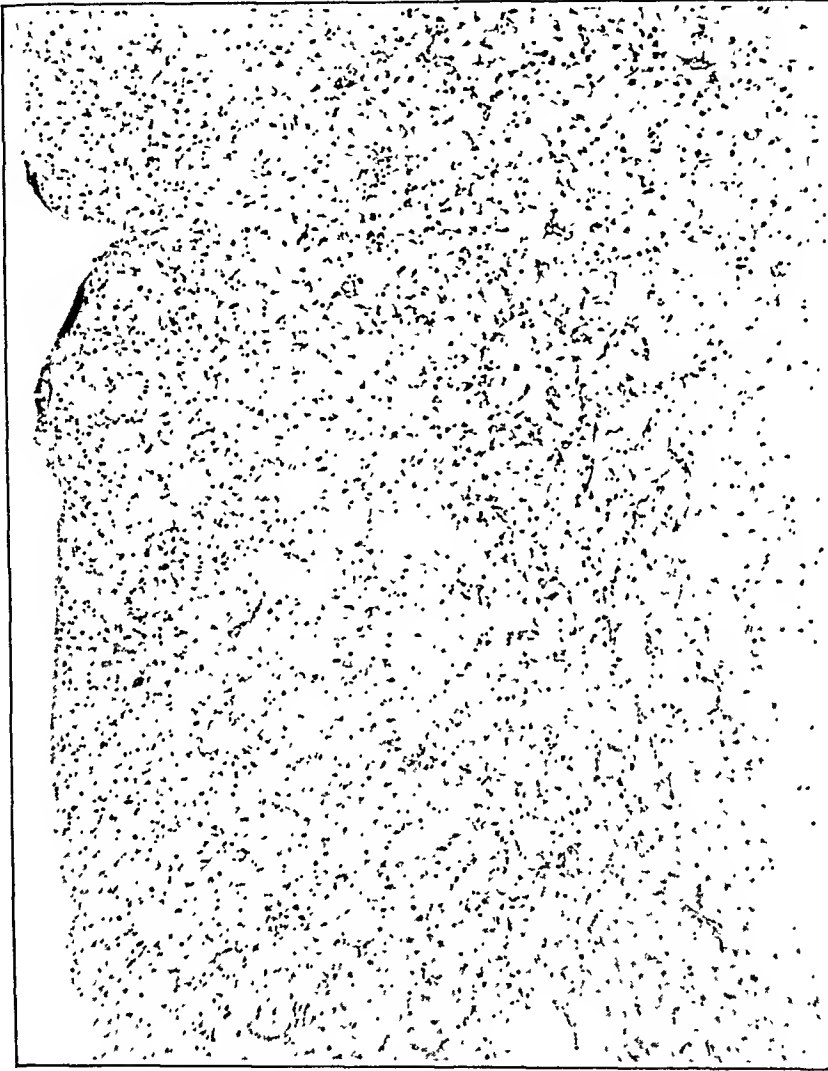


Fig. 5.—Hyperplasia of the astroglia in the third layer of the cerebral cortex of the frontal lobe. Globus method; Leitz ocular 4; objective 3.

Amaurotic family idiocy (Tay-Sachs disease) is distinct from the juvenile form (Spielmeyer-Vogt disease). The juvenile form is characterized by dementia acquired between the ages of 8 and 14 years and by epilepsy, atrophy of the optic nerve and, finally, blindness; often modification of the retinal pigment occurs. The clinical picture that has been described for the juvenile form does not adequately cover all the verified cases of the disease. Though Spielmeyer considered the

clinical diagnosis to be extremely difficult, Sjögren and Sjövall presented what they considered classic pictures and claimed that there were only slight variations in individual cases. According to the latter authors, the child develops normally up to the age of 5 to 8 years. At some time during this period disturbance of vision occurs and symptoms of mental regression are noted. Epileptiform attacks begin and increase, in both frequency and severity. The symptoms referable to the extra-

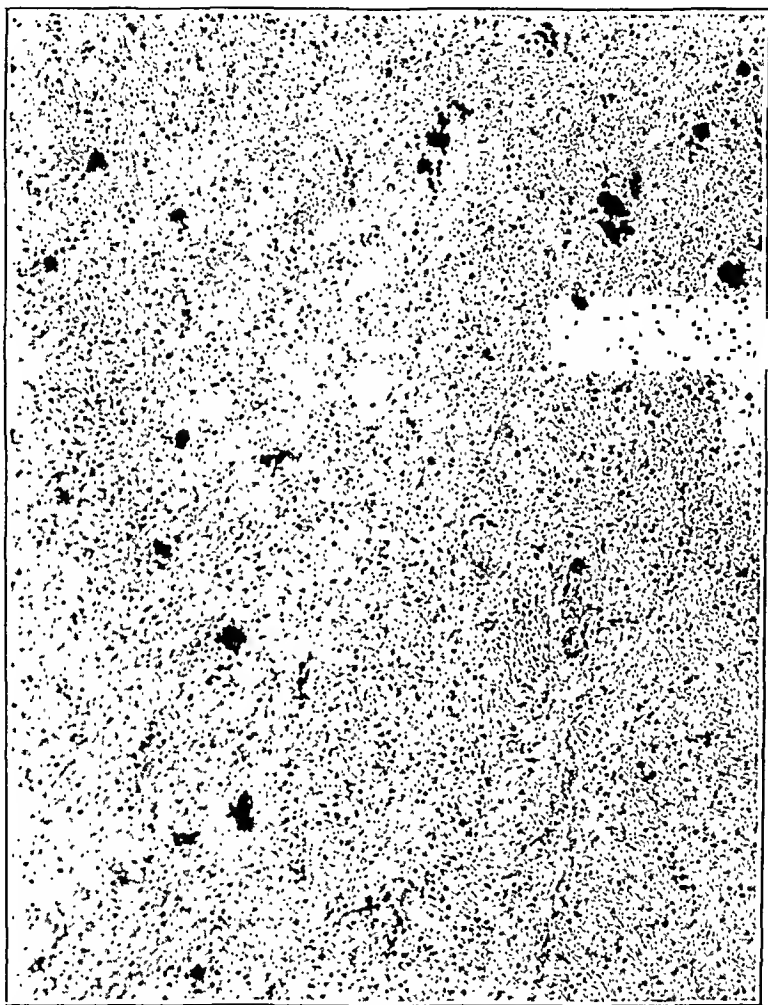


Fig. 6.—Section of the corpus striatum, showing lightly stained, balloon-shaped cells. Nissl method; Leitz ocular 4; objective 5.

pyramidal system then develop; they were said by Sjögren and Sjövall to be the most prominent feature of this form of the disease. The extra-pyramidal involvement results in a constantly increasing rigidity of body posture, loss of associated and automatic movements, retardation and, finally, absence of voluntary movements. If voluntary movement is not completely lost, a disturbance in gait, characterized by short steps, occurs. This is followed by disturbances in equilibrium. As the dis-

ease progresses, paraplegic atrophy of the lower extremities begins; apathy deepens, and then all voluntary movement ceases and the marasmic patient dies of intercurrent disease, usually about the seventeenth year of life.

Pathologically, amaurotic juvenile idiocy can be classified with forms of neuroganglionic degeneration, involving all parts of the neuraxis and varying widely in extent, according to the region affected. It

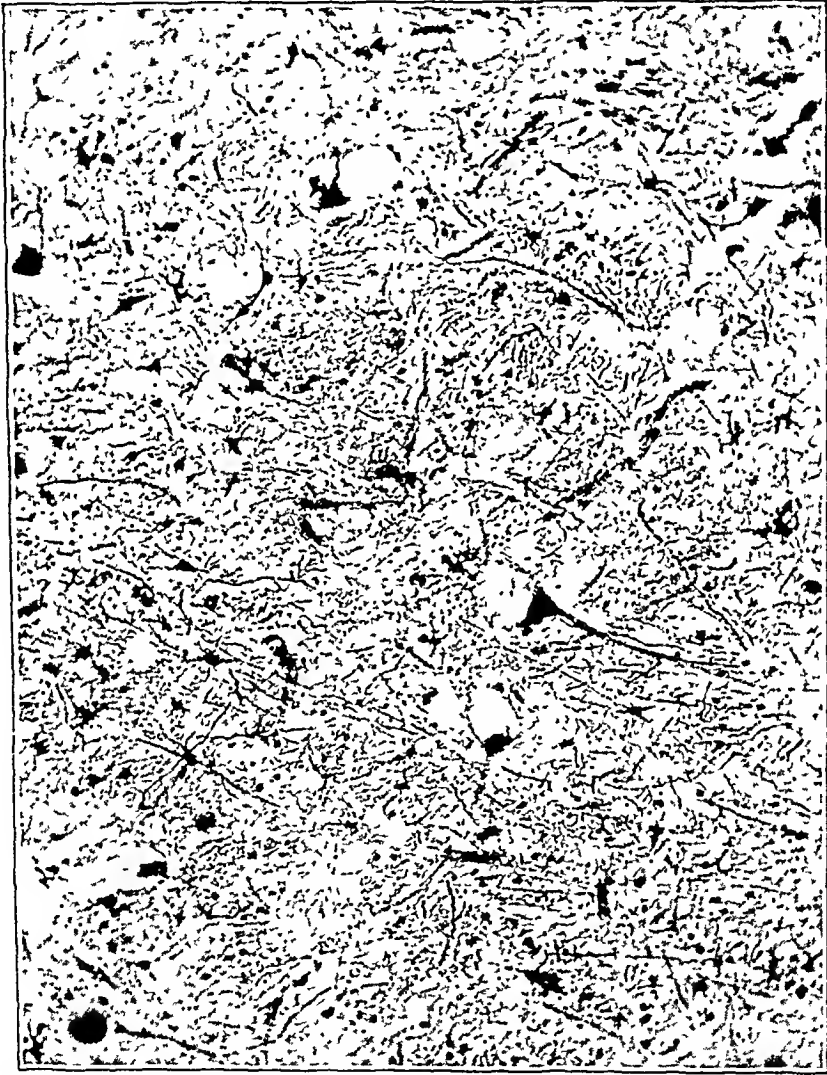


Fig. 7.—Section of the corpus striatum. No hyperplasia of the glia is to be seen. The cells present a balloon-shaped aspect. Globus method; Leitz ocular 4; objective 5.

is these regional variations that probably explain the well defined and diverse clinical types described by various authors.

The pathologic picture shows the characteristic feature that Schaffer⁵ stated to be fundamental in hereditary diseases of the nervous system,

5. Schaffer, C.: Pathogenesis of Amaurotic Idiocy, *Arch. Neurol. & Psychiat.* 24:765-774 (Oct.) 1930; Zur Pathogenesis der Tay-Sachs'schen amaurotischen Idiotie, *Neurol. Centralbl.* 24:386-437, 1905; General Significance of Tay-Sachs Disease, *Arch. Neurol. & Psychiat.* 14:731-741 (Dec.) 1925.

namely, ganglionic selectivity of the pathologic process, the mesodermic elements being completely spared. The pathologic process affects only the tissues derived from the neurectoderm. The condition may therefore be termed a selective germ layer disease. Schaffer stated that the disease involves principally the hyaloplasm of the affected cells; in the cytoplasm without basic structure swelling occurs first. After this,

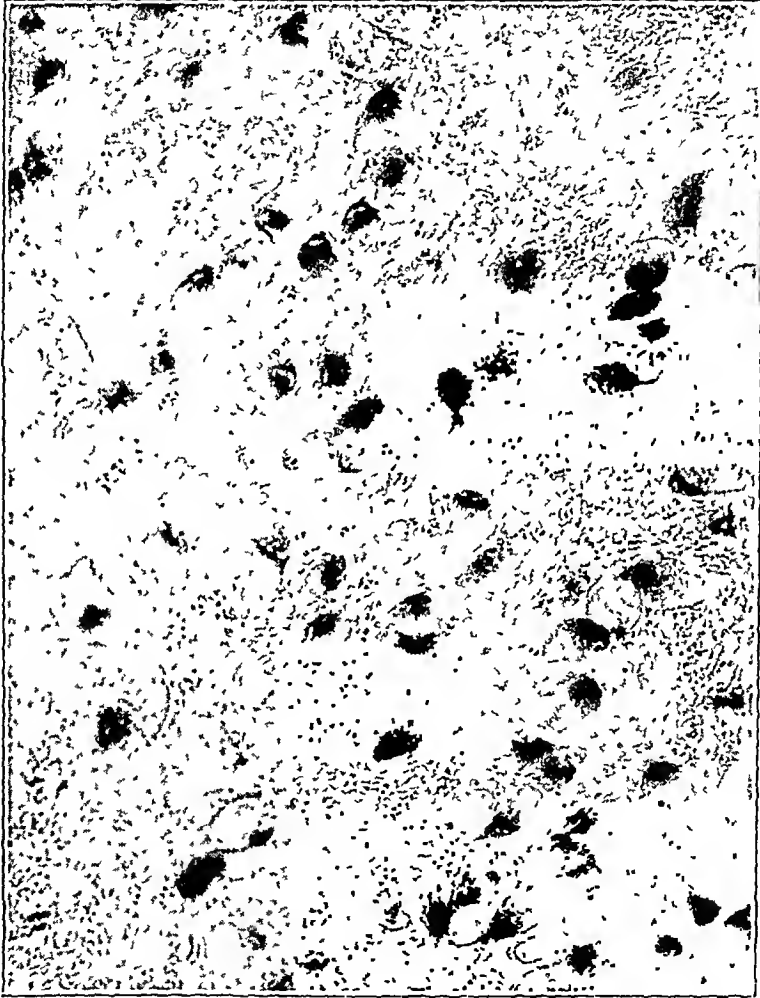


Fig. 8.—Section of the substantia nigra. Balloon-shaped cells are evident; the interstitial tissue appears rarefied and granulated. Nissl method; Leitz ocular 4, objective 5.

a granular material appears, which fills the cytoplasmic area. Schaffer called this material prelipid granules; as disintegration proceeds, these granules are converted into simpler fatty substances. According to Schaffer, the final alteration in this disintegrative process takes place in the body of the glia cells, and these cells act as macrophages. Strauss and Sachs published material that has confirmed both Schaffer's obser-

vations. Recently, further pathologic work on other forms of the disease affecting the cerebellum and the white matter of the brain has been carried out, notably by Globus and Hassin.

The pathologic process in amaurotic family idiocy appears to be ubiquitous and shows a preferential distribution, which distribution is reflected in the clinical picture. The change in the metabolism of the cytoplasm, which centers in the prelipid granules, seems to constitute the

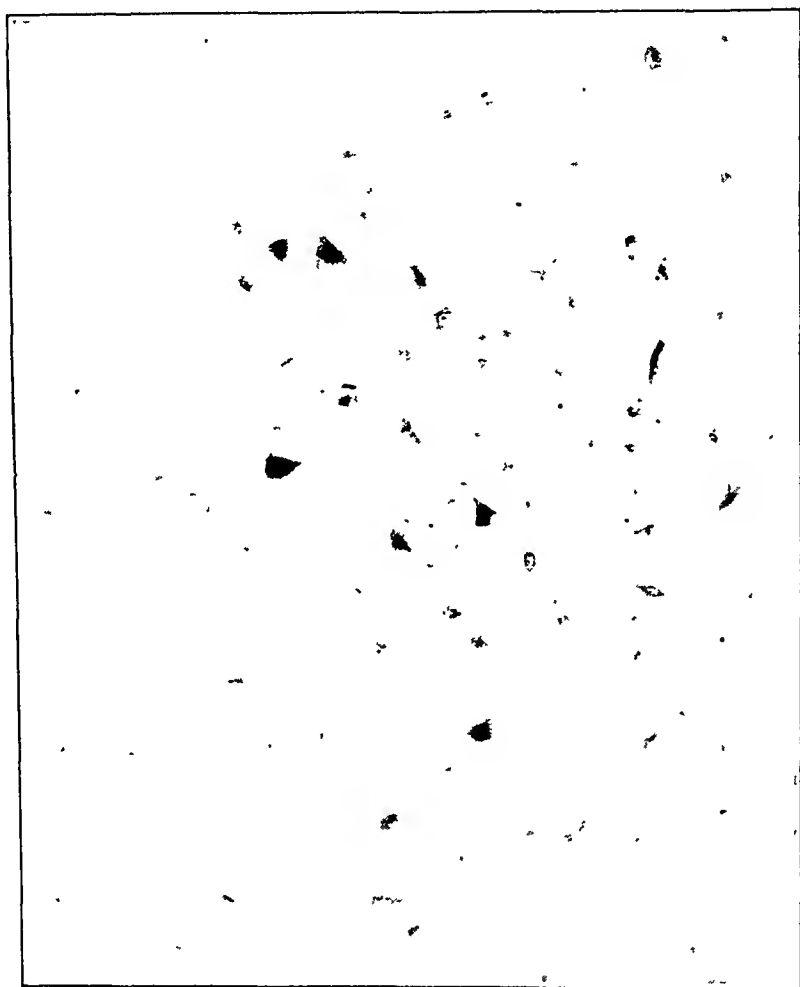


Fig. 9.—Histologic section of the medulla. Balloon-shaped appearance of the cells of the hypoglossal nucleus. Nissl method; Leitz ocular 4; objective 3.

foundation of the pathologic process. This occurs in infancy and progresses, leading always to death. There seems to be a definite relationship between senile involution and amaurotic family idiocy, an analogy which has been noted by Marinescu.

The sudanophilic lipids which are observed in the juvenile form and in other types of amaurotic family idiocy present a picture identical with the pigments observed in senile involution, in the cells of patients dying in the fifth, sixth and seventh decade of life.

SUMMARY

A brief review of amaurotic family idiocy is given, and a case is reported, with results of pathologic examination. The outstanding clinical feature of the case presented was a type of dystonia identical with that observed in Wilson's disease and in the Hallervorden-Spatz syndrome. There was mental deterioration, but no amaurosis or other ophthalmic change.

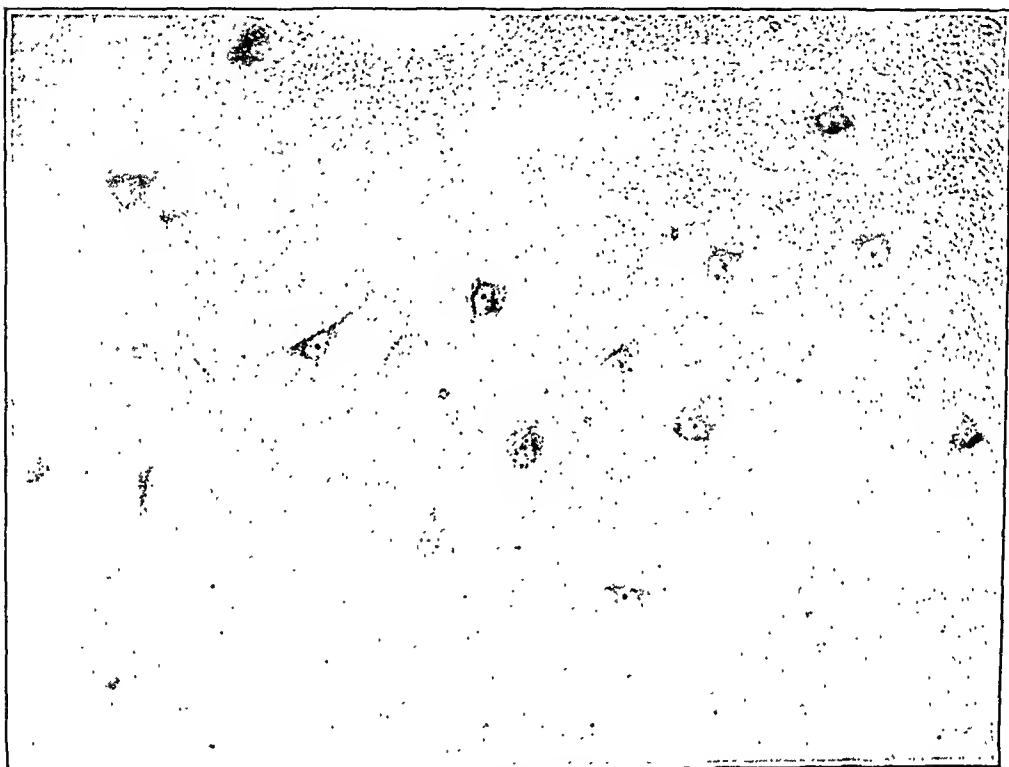


Fig. 10.—Balloon-shaped cells in the anterior horn of the spinal cord. Nissl method; Leitz ocular 4; objective 5.

The diagnosis of amaurotic family idiocy was made possible by histopathologic study, which revealed a pronounced change in the nerve cells in all nerve tissues examined, including the cerebral cortex, corpus striatum, pons, medulla and spinal cord.

It is believed that this process is a heretofore undescribed form of the disease, which might properly be called a dystonic form of amaurotic family idiocy.

Marques de são Vicente 316.

CONGENITAL CYST OF THE SPINAL MENINGES AS CAUSE OF INTERMITTENT COMPRESSION OF THE SPINAL CORD *

RAYMOND D. ADAMS, M.D.

AND

WALTER WEGNER, M.D.

BOSTON

IN RECENT years we have had occasion to observe and study 2 unusual cases in which the spinal cord was intermittently compressed by a solitary cyst in the meninges. The cysts were filled with a mucinous material, were lined with ciliated epithelium and had a wall composed of fibrous connective tissue, bone and cartilage. They were situated in the spinal subarachnoid space, and the one of which the anatomic relationships could be ascertained was connected by a narrow stalk of connective tissue to the dura. Because of their morphologic characteristics, we are inclined to believe that these meningeal cysts are quite different from the usual dermoid, meningocele or meningo-myelocele. Although similar cases have been reported, we ourselves were not hitherto familiar with this condition and believe that the average neurologist is not acquainted with it. The purpose of the present communication is to set these 2 cases on record and to discuss the nature and pathogenesis of this cyst.

REPORT OF CASES

CASE 1.—*History*.—An Italian casket maker aged 41 entered the Boston City Hospital on Sept. 26, 1941, because of pain in the lower part of the back and the buttocks and weakness of the legs. The present illness began in 1928, when for the first time he had a pain in the lumbar region. It came on gradually without antecedent injury and became steadily more intense until he was unable to work. He was admitted to a hospital and a plaster spica was applied, but during the next twenty-five days he obtained no relief from the pain. A tonsillectomy was

From the Neurological and Neurosurgical Service, Boston City Hospital, and the Departments of Neurology and Surgery, Harvard Medical School.

* Dr. Herbert Block, of the Department of the Classics, Harvard College, suggested that this condition be called meningocystitis spinalis congenita. The first word is newly formed and is latinized Greek, and the last two words are Latin adjectives already in common use. Latinized Greek terms are objectionable to purists in language, but their use is customary in medical science. The word "teratomatous," which has been used by other authors to designate this cyst, is pseudo-Greek; its only genuine element is *τέρας*, meaning "monster," and does not imply the congenital nature of the cyst.

then performed, and later "electric treatment" and hydrotherapy were given, without effect. During this illness the right leg was noted to be weak. These symptoms then all subsided spontaneously.

During the next four years the patient remained well, and then, in 1932, the pain recurred in the same region of the back. This time he was in the hospital for seven weeks. Adhesive strapping and local application of heat were used, and the pain disappeared.

In 1935 the patient went to the hospital after having had severe pain in the lumbar region for about ten weeks. The findings on physical examination were said to have been normal, and roentgenograms of the spine and pelvis revealed no abnormalities. After being in the hospital five days, he was discharged as improved. One year later he had an operation for an undescended left testis and inguinal hernia. While he was convalescing, pain in the back recurred, and a plaster spica was applied for six weeks, without benefit. Again, the pain disappeared after a few weeks.

The patient remained well and worked regularly until the summer of 1941, at which time the pain in the back returned. This time it was accompanied with weakness and numbness of the legs. Urgency and precipitancy of urination also developed. He recalled that on one occasion his legs gave way and he collapsed to the floor. At the time of admission to the hospital the pain in the back had extended to the right side of the chest and across the upper abdominal quadrant on the right side.

Examination.—The patient was well developed and appeared healthy. He was oriented and rational and gave an adequate history. The only abnormal physical signs were those referable to the nervous system. The cranial nerves and upper extremities functioned normally. There was moderate weakness of all the muscles of both legs, more pronounced on the right than on the left. The muscles of the right leg were slightly atrophied, especially the quadriceps group, where fascicular twitches were seen. The muscular tone was approximately normal. The abdominal muscles were also weakened, so that the patient was unable to sit up except with the aid of his arms. The knee jerk was absent and the ankle jerk hyperactive (3 plus) on the right side; both reflexes were 2 plus on the left side. The abdominal reflexes were absent, and the plantar reflexes were equivocal, probably extensor in type. On the right side of the body there was pronounced reduction in pain and temperature sensations from the sixth thoracic to the first sacral segment, and from the first sacral to the fifth sacral these sensations were slightly impaired. On the left side pain and temperature sensations were impaired from the first lumbar to the fifth sacral segment. Touch sensation was normal throughout these areas. Vibratory and postural sensations were diminished below the hips. There was tenderness on percussion of the spines of the lower thoracic and lumbar vertebrae.

Laboratory Data.—The blood count and urinalysis gave values within normal limits. The cerebrospinal fluid was under a pressure of 180 mm., was slightly yellow and contained 4 lymphocytes per cubic millimeter and 154 mg. of protein per hundred cubic centimeters. There was a partial dynamic block, as evidenced by the slow fall of pressure after jugular compression. The serologic reactions of the blood and the Wassermann and Davies-Hinton reactions of the spinal fluid were all negative. With injection of 5 cc. of iodized poppyseed oil into the lumbar sac, it was possible to demonstrate a block at the twelfth dorsal vertebra.

Course.—A laminectomy was performed on October 3. There was thinning of the laminae of the eleventh and twelfth thoracic and first lumbar vertebrae,

and the epidural space was reduced. The dura was thin and seemed distended. Beneath the dura was a whitish tumor, which was lightly adherent to both the dura and the arachnoid in some areas. It extended from the lower border of the tenth thoracic to the second lumbar vertebra. This tumor appeared to merge with the cord laterally and could not be dissected free. When incised, it was observed to consist of a thin-walled cyst filled with a whitish mucoid material. When the contents were removed by suction, there was nothing left but a thin, parchment-like shell of the cyst wall. The spinal cord was severely compressed by this cyst. No communication between the central portion of the spinal cord and the cyst could be demonstrated. A catheter was inserted upward and downward in the subdural space without encountering any obstruction.

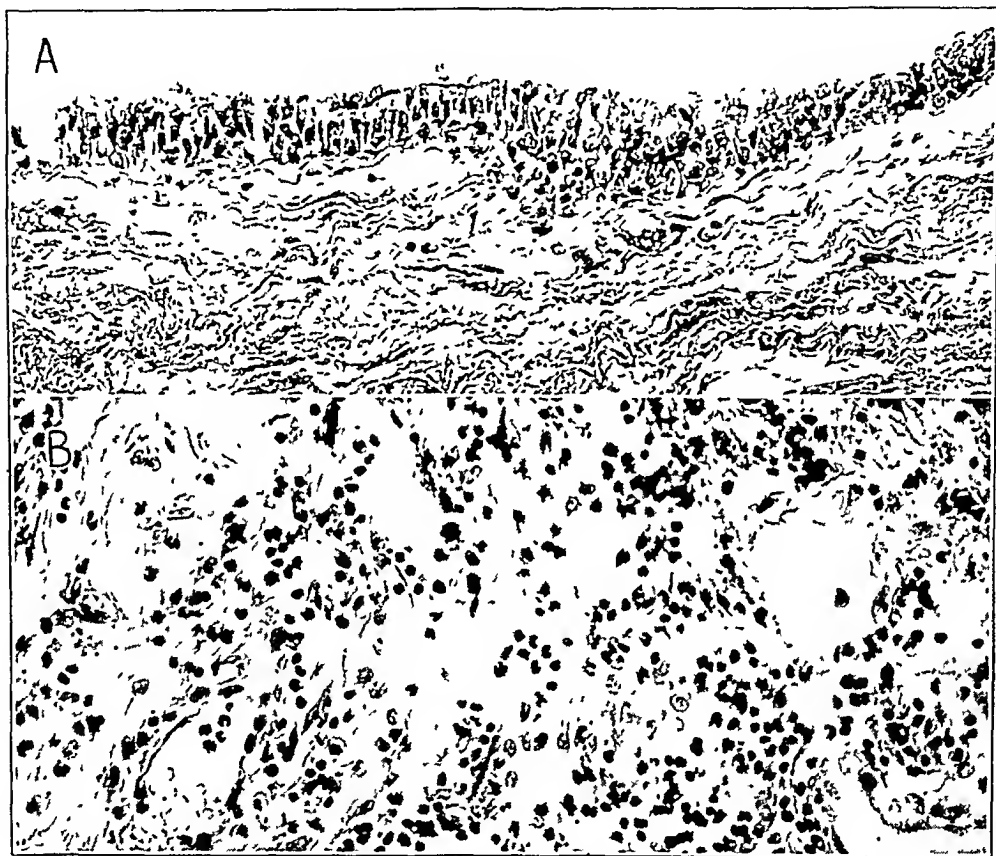


Fig. 1.—*A*, photomicrograph of wall of the cyst, showing fibrous connective tissue and ciliated columnar epithelium; phosphotungstic acid hematoxylin stain. *B*, focus of polymorphonuclear leukocytes, lymphocytes, plasma cells and histiocytes in the wall of the cyst.

The postoperative course was satisfactory, and at the time of the patient's discharge, on October 28, he was free of pain, showed no sensory impairment and was able to walk easily. At this time his bladder did not empty completely; there was a residuum of 150 cc. at the end of urination. Reexamination on December 10 showed that the patient still had slight weakness and flabbiness of the muscles of the right leg. The right ankle jerk was now diminished. He still experienced a mild pain around the lower right part of the thorax, and there was mild hypalgesia from the ninth thoracic to the first lumbar dermatome on the right side. He returned to his job at this time. When last seen on April 7, 1942, he had no complaints except for mild weakness in the right leg.

Pathologic Observations.—Several small pieces of the wall of the cyst were submitted for histologic examination. The wall was composed of collagenous connective tissue, in which there were numerous small arteries and veins and, in one place, a fascicle of nerve fibers. The cyst was lined with ciliated epithelium (fig. 1 *A*); the lining had a thickness of several cell layers. In places the connective tissue was infiltrated with polymorphonuclear leukocytes and macrophages. Fibroblasts were actively proliferating in these regions (fig. 1 *B*). Focal collections of lymphocytes and plasma cells were also present. There was no glial tissue in the wall. The pathologic diagnosis was teratomatous cyst of the spinal meninges.

CASE 2.—History.—A man aged 29 was admitted to the hospital on Dec. 6, 1945, because of paralysis of his arms and legs and difficulty in breathing. In the past six years he had had at least five episodes similar to the one which led to his latest admission to the hospital.

In July 1939 he first began to have a rather severe pain in his neck. About the time of onset of the pain he had fallen downstairs, but the accident did not seem to bear a causal relationship to his symptoms. Then, over a period of a few days, his right arm and both legs became paralyzed. On the day of his admission to the hospital his left arm also became paralyzed. Examination at this time disclosed a patient who was drowsy and confused. There were no abnormalities of the cranial nerves. The right arm and leg were completely paralyzed, and the left limbs were so weak that only a few feeble movements were possible. The paralyzed muscles were of normal bulk and were flaccid. All the tendon reflexes were obtainable, though sluggish; the plantar reflex was equivocal on the right and absent on the left. No definite sensory changes could be detected. The cerebrospinal fluid was under a pressure of 250 mm. of water; the fluid was slightly yellow; it contained no cells, but the total protein was 249 mg. per hundred cubic centimeters. The patient was placed in a respirator, and no further progression of neurologic symptoms occurred. He began to improve during the fourth week in the hospital. Subsequent lumbar punctures on August 24 and September 8 revealed total protein values of 59 and 25 mg. per hundred cubic centimeters, respectively, and the dynamic pressure was said to be normal on both occasions. At the time of discharge the patient still showed great weakness of his limbs, more pronounced on the right side, but was able to walk with assistance. He returned to his home, and within a few weeks he had recovered normal control of his limbs. The only residual symptom was a slight dragging of the right leg when fatigued. The only two clinical diagnoses which were seriously considered were acute infectious polyneuritis and acute multiple sclerosis.

One year later the patient had recurrence of the pain in his neck and weakness of the right arm, which lasted one week. In June 1943 he began to experience a burning pain in the right side of his neck and within a few days had almost complete paralysis of all four extremities. The order of paralysis was again the right arm, right leg, left leg, trunk and left arm. There were no paresthesias in the right hand. Examination at this time (June 15) showed an alert, well oriented man, whose neck was rather stiff. The right pupil was smaller than the left, and sweating was reduced over the right side of the face. All extremities were completely paralyzed. There were slight atrophy and some spasticity of the right arm and leg. Tendon reflexes on the right side were 3 plus, whereas those on the left side was 2 plus. The right plantar reflex was extensor and the left one flexor. The patient was incontinent of urine and feces. There was impairment of all forms of sensation below the fourth cervical segment. The dynamic pressure of the spinal fluid was said to have been normal, and the total protein content was 364 mg. per hundred cubic centimeters; there were no cells, and the Wassermann reaction was negative. On June 23 the total protein was

444 mg.; on June 28 it was 375 mg. and on July 15 it had fallen to 25 mg., per hundred cubic centimeters. Thrombophlebitis developed in the left leg in the early part of July, and on July 9 bilateral ligation of the saphenous vein was done. The paralysis became more pronounced until it was impossible for the patient to make a single movement of any part of his body. By September 11, however, considerable improvement was noted, and this continued, so that by November 6 he was able to walk if assisted by two persons. At this time the tendon reflexes were still hyperactive on the right side and the plantar reflexes were extensor bilaterally. Sensory impairment was less severe, being now greatest in the left leg. At the time of his discharge, on December 18, there were still weakness of all four extremities and slight atrophy of muscles in the right leg. A tentative diagnosis of multiple sclerosis was made at the time of discharge. At home the improvement continued, and within two or three months the patient had completely recovered except for easy fatigability of the right leg.

In April 1944 the patient had an infection of the upper respiratory tract, which was followed by weakness of all four extremities. He remained at home in bed for three weeks with partial paralysis of his limbs and some urinary incontinence, but after a short time was able to get about once again. In September 1945 there was another episode of weakness of the right arm and both legs, which lasted about two or three weeks.

In November 1945 the patient again had an infection of the upper respiratory tract, and afterward his right leg dragged more than usual. He had pain in the right side of his neck. He became extremely constipated and had to resort to enemas. During the next two weeks the fingers of the right hand became numb and paralyzed, and in another three days both legs and the left arm became weak and numb. The patient was by this time incontinent. Spontaneous flexor spasms of the right arm and leg occurred intermittently. He was brought to the hospital because of respiratory difficulty, which had developed a few hours before admission.

Examination.—The temperature, pulse and blood pressure were normal. Respirations were shallow and depended entirely on movements of the diaphragm; the intercostal muscles were paralyzed. The patient was frightened and slightly confused. Shrugging of the shoulders was the only movement of the trunk or limbs of which he was capable. The legs were slightly spastic and in a position of extension. All the tendon reflexes were of about 3 plus activity and were brisker on the right side than on the left. The abdominal reflexes were absent; the right plantar reflex was extensor, while the left one was flexor. All forms of cutaneous sensation were absent on the right side below the fourth cervical dermatome and were impaired in a similar area on the left side. Vibratory sensation was partially retained in the hands and over the upper thoracic portion of the spine but was absent below this point. Postural sense was absent in the lower extremities and reduced in the hands and arms.

Laboratory Data.—The blood count and urinalysis revealed no significant abnormalities. The initial pressure of the cerebrospinal fluid was 205 mm. and the dynamic pressure was normal; the total protein was 78 mg. per hundred cubic centimeters; there were no cells, and the Wassermann reaction was negative. Roentgenograms of the cervical portion of the spine showed slight thinning of the pedicles of the third, fourth and fifth vertebrae.

Course.—Because the neurologic symptoms were, and had been, all referable to a single lesion in the cervical portion of the spinal cord and the spinal fluid protein was consistently elevated at the time of the paralysis, it was decided to make a myelographic examination. An ovoid defect was visualized when the "pantopaque" (an iodized poppyseed oil with special adhesive properties) reached

the level of the fourth cervical vertebra (fig. 2). A laminectomy was performed on Jan. 22, 1946 and exposed a grayish mass lying under the dura on the right dorsilateral surface of the spinal cord. It was surrounded by a thin membrane, as though the arachnoid had split to encompass it. Dorsally the tumor and membrane were so tightly adherent to the dura that part of the dura was removed with the tumor. The tumor was fluctuant and obviously cystic. Attached to the right anterolateral side of the tumor was a structure having the appearance of a nerve root filament, but it was not sensitive to manipulation like the other nerve roots. Although it seemed to leave the canal with the other filaments of the fourth cervical nerve root, it first made a detour caudal to the attachment of the dentate ligament at that level, whereas the other filaments



Fig. 2—Lateral view of the cervical portion of the spine, showing the cyst at the fourth cervical vertebra outlined with "pantopaque."

passed cephalad to the attachment. There was no evidence that this structure passed through the tumor and joined the spinal cord, and it was therefore regarded as a pedicle of the tumor attaching it to the dura. The tumor measured 2 by 2 by 1 cm. and compressed the spinal cord. This cystic mass was completely removed, without rupture of the wall.

The patient's postoperative course was uneventful, and within a few days he began to improve. He was discharged from the hospital one month after operation, being able at this time to walk with slight assistance but still showing considerable weakness and spasticity in all extremities.

Pathologic Observations.—The wall of this cyst was semitransparent and grayish white. It was composed of rather tough fibrous tissue. The contents of

the cyst were fluid and tended to string out as mucinous material does; this material was grayish white. A smear of the contents of the cyst showed only amorphous material, containing a few poorly preserved cells. The material gave positive chemical reactions for mucin. Microscopic section of this cyst revealed

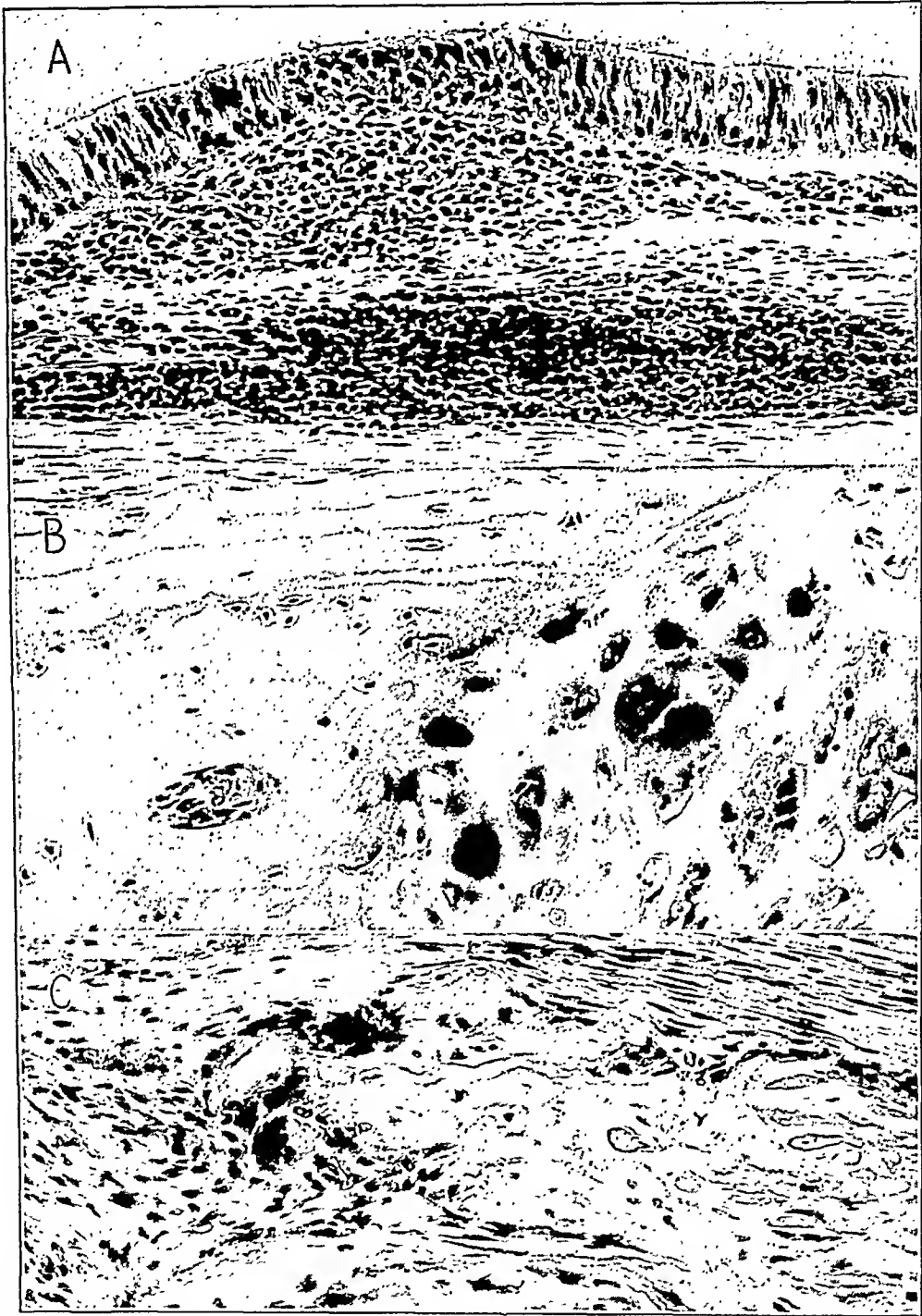


Fig. 3.—Photomicrograph of the wall of the cyst, showing (A) ciliated columnar epithelium and focus of lymphocytes in the wall of the cyst, (B) hyaline cartilage and bone beneath the epithelial lining of the cyst and (C) mucinous material in the wall of the cyst, surrounded with macrophages and foreign body giant cells.

that the wall was composed of collagenous connective tissue and, in places, bone and cartilage. Grayish, mucinous material surrounded by macrophages and foreign body giant cells (fig. 3 C) could be seen in some parts of the wall. At one place

a nerve twig could be seen within the wall of the cyst. The lining was composed of a columnar, ciliated epithelium. Just beneath the epithelium there were focal collections of lymphocytes and macrophages. With the phosphotungstic acid stain there were no glial fibrils. The total thickness of the wall of the cyst was from 0.5 to 1 mm.

Diagnosis.—The diagnosis was teratomatous cyst of the spinal meninges.

COMMENT

The Clinical Syndrome.—The outstanding clinical features of these 2 cases were the intermittent pain and the paralysis. In case 1 there were five attacks of pain in the lumbar portion of the back, in two of which there were weakness of the legs, sensory impairment and partial paralysis of the bladder and rectum. In the second case there were five attacks of cervical pain, followed by hemiplegia or quadriplegia with sensory paralysis and paralysis of the bladder and rectum. In each attack the symptoms were of subacute onset and development progressed to a certain point, and the process then underwent fairly complete recession. Between attacks, even though the paralysis had been almost complete, the patient was almost entirely free of symptoms.

The clinical syndrome was essentially that of a transverse lesion of the cord of reversible character, in the thoracic region in 1 case and in the cervical region in the other. The distribution of motor and sensory paralysis was the same in each attack. One side was always affected more than the other, and in case 2 the pattern of motor involvement was always in the order of the right arm, right leg, left leg and left arm. When the paralysis was incomplete a partial Brown-Séquard syndrome was present. The recovery from sensory and motor paralysis was always in reverse order; i. e., the parts last paralyzed were the first to move. Motor symptoms usually preceded sensory symptoms and, if the attack was not very severe, were the only symptoms present. Recovery from motor paralysis was always slower than that from sensory paralysis. In case 1 there was a tendency toward segmental sensory dislocation in the last attack; the loss of pain and temperature sensibility was greater over the lower thoracic and lumbar segments than over the sacral ones. Touch sensation was always affected less than pain and temperature sense. The bladder and rectum were paralyzed only when motor paralysis involved both sides of the body.

Pathophysiologic Changes.—In these cases, particularly in case 2, there were manifested in an almost perfect natural experiment the effects of hydrodynamic compression of the spinal cord. This caused pain over the spine, probably due to stretching of the meninges, and in case 2 root pain. One side of the cord was observed to be compressed more than the other, accounting for the asymmetry of the sensory and motor paralysis and the partial Brown-Séquard syndrome. The increased spinal fluid protein and the partial dynamic block in

case 1 were caused by obstruction of the spinal subarachnoid space. In case 2, even though there was a high protein content, the cyst was so soft that it transmitted the intracranial pressure.

The cause of the intermittent swelling of the cysts is an intriguing problem. Four possible explanations occur to us: 1. The wall of the cyst ruptured when the pressure reached a certain point, and the contents escaped into the subarachnoid space. 2. The wall of the cyst broke under the increasing pressure of accumulated secretions, and the contents of the cyst escaped into the wall of the cyst, being removed by macrophages and giant cells. 3. The mucinous contents were resorbed by the same cells which secreted them. 4. The cystic fluid was in osmotic relation to the blood and was therefore influenced by hemodilution or by congestion of meningeal vessels of whatever cause, and possibly by other factors. The first possibility seems unlikely because the wall of the cyst was tough and because there was at no time any meningeal irritation, as would be expected from a sudden escape of mucinous secretion into the subarachnoid space. Although the presence of macrophages and giant cells around homogeneous material in the vessel wall supports the second hypothesis, it seems improbable to us that the cyst could be effectively decompressed by this means. The most plausible explanation is that the rate of mucinous formation and absorption is influenced by hydration of the blood or by congestion of meningeal vessels. It is interesting in this connection that in case 2 the last three attacks were preceded by an infection of the respiratory tract. Swelling of cerebral tumors and of cerebral cysts before the menstrual period and with infection has been observed and commented on by numerous authors. Our pathologic material does not permit a final decision on this matter.

The differential diagnosis of an intermittent solitary lesion of the spinal cord includes relatively few diseases. Acute myelitis or multiple sclerosis can, of course, produce over a relatively short period symptoms referable to the spinal cord which will undergo spontaneous remission. This was the diagnosis entertained for a year or two in the second case. If, however, one insists on the cardinal criteria of multiple sclerosis, namely, that the lesions be disseminate in their distribution as well as discontinuous in time, this diagnosis cannot be validated. Further, the extremely high protein content of the spinal fluid and, in the first case, the dynamic block with each exacerbation of the disease are not seen in cases of multiple sclerosis. A ruptured cervical or thoracic disk may at times compress the cord intermittently. Cases have been reported in which after each of several successive traumas to the spine symptoms referable to the spinal cord have been produced, only to subside on immobilization of the spine. The spontaneous nature of the symptoms in our cases and their subacute evolution

in each attack were decidedly against this possibility. Spinal adhesive arachnoiditis may at times cause symptoms which progress up to a point and then undergo partial remission, only to recur with a subsequent infection. This was the diagnosis most seriously considered in the first case. However, the discreteness of the lesion and the complete remission of symptoms between attacks tended to exclude both this disease and multiple sclerosis. The second objection could also be raised against an aneurysm of the anterior spinal artery. Repeated dislocation of the atlas on the axis, which may occur in young people and cause compression of the cervical portion of the cord with sensory and motor paralysis and respiratory difficulty, may simulate a spinal meningeal cyst. In our cases the lower level of involvement of the spinal cord and the normal appearance of the spine in lateral roentgenograms excluded this condition. Syringomyelia and myelodysplasia were suggested by the sensory changes in case 1, but the intermittent course of the disease justified rejection of this possibility.

Origin of the Cysts.—The genesis and classification of cysts of this character regardless of their location have been subjects of much speculation. Many observers have pointed out the similarity of the lining of ciliated columnar epithelium to the epithelium of the respiratory tract and the fetal gut, or even to fetal ependyma. The representation of tissues derived from the ectodermal and mesodermal germ layers indicates that these tumors are not the result of mechanical displacement of ectodermal elements during fetal life, such as occurs in the dermoid or epidermoid tumors but, rather, are complex teratomatous neoplasms caused by a dislocation of pluripotential cells during early embryonic life. This explanation has been accepted by Kubie and Fulton,¹ by Hosoi² and by Bucy and Buchanan³ and seems most plausible. The relationship between these cysts and myelodysplasia or other defects in closure of the neural tube is unsettled. Because of the absence of obvious connection with the spinal cord in some cases and the absence of glial elements in the wall of the cyst, we prefer to view these tumors as true teratomas which may in some instances be associated with a congenital malformation of the spinal cord.

Review of the Literature.—We have found 6 other cases in the medical literature which closely resemble the 2 cases reported here. Seven additional cases are described in the publications of Gowers and

1. Kubie, L. S., and Fulton, J. F.: Clinical and Pathological Study of Two Teratomatous Cysts of Spinal Cord, Containing Mucus and Ciliated Cells, *Surg., Gynec. & Obst.* **47**:297-311 (Sept.) 1928.

2. Hosoi, K.: Intradural Teratoid Tumors of Spinal Cord: Report of Case, *Arch. Path.* **11**:875-883 (June) 1931.

3. Bucy, P. C., and Buchanan, D. N.: Teratoma of Spinal Cord, *Surg., Gynec. & Obst.* **60**:1137-1144 (June) 1935.

Horsley,⁴ Gerlach,⁵ Forbes,⁶ Frick,⁷ Thomas and Quercy,⁸ Bielschowsky and Unger⁹ and Hansmann¹⁰ of teratomas of the spinal cord, but they differed in that the tumors were not cystic, did not produce symptoms intermittently and were in some instances associated with myelodysplasia.

In 1928 Kubie and Fulton¹ described in detail 2 cases of teratomatous cyst of the spinal cord which was successfully removed at operation. The cyst in each case was solitary, was situated in the spinal sub-arachnoid space without attachment to the spinal cord, was lined with a ciliated columnar epithelium and had in its wall mucous and serous glands, smooth muscle, nerve fibers, bone and cartilage. Case 1 was that of a child aged 2 years who had weakness of the right leg and a "tender" abdomen. Roentgenograms disclosed occult spina bifida of the lower thoracic, lumbar and sacral vertebrae. With lumbar puncture between the tenth and the eleventh thoracic vertebra, a thick, "egg-white" fluid filled with ciliated cells was obtained. At operation a large flattened cyst was observed extending from the tenth dorsal to the fourth lumbar vertebra. The child recovered completely. Case 2 was almost exactly like our second case. The patient, a white woman aged 27, had had five attacks of left hemiplegia with pain in the left cervical region and the Brown-Séquard type of dissociation of sensation in the trunk and extremities at varying intervals since the age of 21. In her last attack there was almost complete quadriplegia with an upper level of sensory disturbance at the fourth cervical dermatome and grave embarrassment of respiration. At operation a cyst was observed attached to the meninges of the cord at the fourth cervical segment on the left side. The authors expressed the belief that both cysts were congenital and probably represented ependymal diverticula of the spinal cord.

4. Gowers, W. R., and Horsley, V.: A Case of Tumor of the Spinal Cord: Removal; Recovery, *Med.-Chir. Tr.*, London **71**:377-430, 1888.

5. Gerlach, W.: Ein Fall von congenitaler Syringomyelie mit intramedullärer Teratombildung, *Deutsche Ztschr. f. Nervenhe.* **5**:271-301, 1894.

6. Forbes, J. G.: Intra-Medullary Teratoma of the Spinal Cord, *St. Barth. Hosp. Rep.* (1905) **41**:221-232, 1906.

7. Frick, K.: Ueber ein Teratom des Rückenmarkes, *Frankfurt. Ztschr. f. Path.* **7**:127-134, 1911.

8. Thomas, A., and Quercy: Syringomyélie, hyperplasie due tissu conjonctif, fibres musculaires striées dans la moelle, *Nouv. iconog. de la Salpêtrière* **25**:364-383, 1913.

9. Bielschowsky, M., and Unger, E.: Syringomyelie mit Teratom- und extra-medullärer Blastombildung: Zur Kenntnis der Pathogenese der Syringomyelie, *J. f. Psychol. u. Neurol.* **25**:173-218, 1920.

10. Hansmann, G. H.: Congenital Cystic Tumor of Neurenteric Canal with Special Reference to Its Histology and Pathological Significance, *Surg., Gynec. & Obst.* **42**:124-127 (Jan.) 1926.

Hosoi,² in 1931, described with full clinical details a case of intradural teratoid tumor of the spinal cord in the lumbar region. There was occult spina bifida at the fifth lumbar level. The patient gave a vague history of transient paralysis of the legs during childhood, after which he was well until the age of 25, when over a period of two to three weeks there developed pain in the back, weakness of the legs, sensory impairment in one leg and urinary and fecal retention. There were dynamic block of the cerebrospinal fluid and xanthochromia with a very high protein content. Most of the tumor was removed, and the patient recovered almost completely within a few months. Microscopic sections of the tumor revealed smooth muscle cells, fibrous connective tissue, numerous mucous glands and pacinian corpuscles.

In 1934 Puusepp¹¹ reported a case of teratoma of the spinal cord that was almost exactly like the second case of Kubie and Fulton and our second case. The patient was a young adult who had had several isolated attacks of pain in the neck, motor and sensory paralysis in all four extremities and sphincteric disturbances between the ages of 5 and 27 years. A cystic tumor of the spinal meninges in the cervical region which was attached to the dura was successfully removed.

Bucy and Buchanan,³ in 1935, described a teratoma occurring in an infant 16 months of age. The only symptoms were irritability, anorexia and slowly developing paraplegia. The cerebrospinal fluid was yellow, contained abnormally large amounts of protein and clotted spontaneously (Froin's syndrome). Laminectomy disclosed a cyst beneath the dura and compressing the spinal cord from the eleventh dorsal to the fourth lumbar vertebra. The cyst was filled with thick, tenacious, glairy material. At one point the cyst appeared to be attached to the dorsal surface of the spinal cord. Microscopic sections of the cyst showed that it was lined with ciliated cuboidal epithelium and goblet cells, and in a mural nodule there were hyaline cartilage and mucous glands.

Masten,¹² in 1940, reported another case in which a cystic teratoma of the spinal cord was observed at operation. The patient, a 5 year old girl, had had pain in the neck and arms and stiffness of the neck for three weeks and had right hemiparesis affecting the arm and leg on the day of admission. Sensation could not be tested. There were a partial dynamic block of the cerebrospinal fluid and a total protein of 1,200 mg. per hundred cubic centimeters. Operation revealed a cystic tumor beneath the dura from the fourth cervical to the first

11. Puusepp, L.: Variété rare de tératome sous-dural de la région cervicale (intestinome); quadriplégie; extirpation; guérison complète, *Rev. neurol.* **2**:879-886 (Dec.) 1934.

12. Masten, M. G.: Teratoma of Spinal Cord, *Arch. Path.* **30**:755-761 (Sept.) 1940.

dorsal vertebra. During its removal the cyst ruptured and a grayish, sticky fluid was discharged. The patient died on the third postoperative day of bronchopneumonia. . Postmortem examination revealed evidence of compression of the spinal cord. There is no mention of any congenital abnormality of the spinal cord, though the neurosurgeon thought that the tumor was attached to the dorsal surface of the cord.

SUMMARY

Two unusual cases of intermittent compression of the spinal cord by a teratomatous cyst in the meninges are described. Case 1 was that of a white man aged 41 who had had five attacks of pain in the back and partial paraplegia with sensory loss and sphincteric disorder. Case 2 was that of a white man aged 29 who had had five attacks of pain in the neck followed by hemiplegia or quadriplegia, sensory impairment below the lesion, paralysis of the bladder and rectum and respiratory embarrassment. The cerebrospinal fluid protein was increased, and in case 1 there was a dynamic block. In case 1 the cyst was partially removed, and in case 2 it was completely removed, with excellent therapeutic results in both. Microscopic examination of the cysts established their teratomatous nature.

The clinical syndrome is unique. We know of no other spontaneous lesion which will produce compression of the spinal cord intermittently. However, this condition has been mistaken in some instances for ruptured cervical disk, recurrent atlantoaxial dislocation, multiple sclerosis and chronic adhesive arachnoiditis. The mechanism of production of symptoms is swelling of the cyst and compression of the spinal cord. The origin of the cyst is thought to be a displacement of pluripotential cells during early embryonic life and the formation during childhood or adult life of a benign tumor composed of several different structures.

818 Harrison Avenue.

Clinical Notes

PHOTIC DRIVING AS A CAUSE OF CLINICAL SEIZURES IN EPILEPTIC PATIENTS

STANLEY COBB, M.D., BOSTON

The effect of visual stimuli on the electroencephalogram has been of interest since the earliest work on cerebral potentials. Berger noted changes in alpha rhythm following retinal stimulation. Walker¹ and others have studied the effect on the electroencephalogram of intermittent photic stimulation of the retina. The electroencephalogram obtained from the occipital cortex may take on a frequency synchronous with the flicker. This is called photic driving. Moreover, Walker and his associates stated:

. . . If intermittent photic stimuli are allowed to fall suddenly on the retina, one encounters a peculiar hump and spike arrangement which persists for the first six or eight stimuli, after which the waves assume a more sinusoidal form. This peculiar hump and spike formation may be seen at almost any frequency, but is particularly well demonstrated when the frequency of the intermittent photic stimulus is approximately 6 per second.¹

Figure 10 of the paper by Walker and co-workers shows these "spike and hump" responses. They bear a remarkable resemblance to the common wave form of the electroencephalogram in cases of petit mal when short lapses of consciousness appear. It was thought that this resemblance made pertinent 3 clinical observations in which epileptic patients had experienced a lapse of consciousness after exposure to flickering light.

CASE 1.—A girl aged 17 was admitted to the Boston City Hospital in January 1931 with the complaint of "lapses" in which she lost contact for a few seconds. She first noticed these spells at the age of 11, and they gradually became commoner and severer. When she was 13 other people noticed them, and at school she was teased for "absent mindedness" and was nicknamed "lapsey." She had had one convulsive seizure in which she fell, bit her tongue and lost consciousness for five minutes. This occurred two weeks prior to admission and was ushered in by an unusual series of her petit mal attacks. When quiet and at peace she has few attacks; when disturbed by emotional stress, as at dances or examinations, she is likely to have many. She has noticed that flickering light bothers her and is likely to bring on repeated petit mal seizures. For example, leading up to a house which she frequently visits is a long avenue flanked by tall trees arranged in rows. When the sun is low and slanting through the trees any one riding up the avenue in an automobile is exposed to flickering light. This situation has several times caused the patient to have repeated petit mal attacks, culminating in a dazed state when she reached the house.

From the Department of Neuropathology, Harvard Medical School, and the Department of Psychiatry, Massachusetts General Hospital.

1. Walker, A. E.; Woolf, J. I.; Halstead, W. C., and Case, T. J.: Photic Driving, *Arch. Neurol. & Psychiat.* 52:117 (Aug.) 1944.

CASE 2.—A woman aged 50, of superior intelligence and education, came to my office in January 1944 to talk to me about her epileptic niece. She has a sister with migraine. After discussing the niece, she asked me about herself, saying: "I myself have had one convulsion, a few hours after my son was born. Never before nor since; but I had a peculiar experience once. I was standing outside a village store in the evening. The arc light overhead suddenly began to flicker. It went on and on. I felt queer, and suddenly my vision was wiped out. I did not know where I was or what was happening for a few seconds. I did not fall; I just went blank for a short while."

CASE 3.—A clerk of 33 came to the office in May 1946 with the complaint of epileptic fits occurring about once a month at night. A careful history revealed that he had a severe head injury at the age of 13. He had a "spell of unconsciousness" about a year later and another at the age of 16. He was then given phenobarbital and had no seizures until the beginning of the present illness. When pressed to be exact, he said: "Well, I had two funny spells in college at about the age of 19." He experimented in a physics laboratory with a light that gave interrupted flickers at a rapid rate. While working with this, he twice began to feel confused and then went into a short period of unconsciousness without convulsive movements. His electroencephalogram in 1946 showed some low voltage waves at 6 per second frequency.

These clinical observations suggest the importance of investigating the effect of flickering light on epileptic patients, using various rates of flicker for patients with various types of electroencephalograms.

Massachusetts General Hospital.

Obituaries

JOHN FAVILL, M.D.

1886-1946

Dr. John Favill was born Sept. 9, 1886, at Madison, Wis., to Dr. Henry Baird Favill and his wife, Susan Pratt Favill. On the maternal line there were many generations of New Englanders, and on the paternal side there was the heritage of generations of colonial English, to which the blood of an Ottawa Indian chieftain had entered some five generations before him. There was something of the Indian in John Favill. It was evident not only in the prominent cheekbones and the suggestion of native coloring, but also in the softness of his step, his slowness to speak, his freedom from verbosity and his love of and interest in the laws of the natural universe. Both father and son were proud of this heritage.

The Favill family moved to Chicago in 1894, where John completed his preparatory education. From 1894 to 1900 he attended Cobb's School. He graduated from Coultier's University School in 1905. His college education was completed at Yale in 1909. He studied medicine at Harvard Medical School, from which he graduated *cum laude* in 1913. After an internship at Massachusetts General Hospital, Dr. Favill returned to Chicago to associate himself with his father in the practice of internal medicine, being licensed to practice in 1915. In 1917 he was commissioned a first lieutenant in the Army Medical Corps and served chiefly with United States Base Hospital no. 14, the unit from St. Luke's hospital, where he had been a member of the staff. It was during his military service that his interest in neurology was stimulated, so that after his return he entered actively into this field of medicine. He was discharged from the Army in 1919, having received the rank of captain. While Dr. Favill was unable to take an active part in World War II, much of his effort was spent in preparation for such service.

To his profession and his chosen specialty he gave his efforts. On his return to Chicago, he became a member of the staff of St. Luke's Hospital and began his long career of teaching at Rush Medical College. In recognition of his efforts in the hospital, he rose to be senior neurologist in 1928 and held executive positions on the staff. In 1937 he transferred his hospital connections to the Presbyterian Hospital. Here he was attending neurologist and psychiatrist until his death, becoming

chief of the division in 1945. His ability as a teacher brought him recognition. Beginning as an assistant in medicine in 1915, he attained the rank of professor of neurology in 1934, which rank he continued to hold when Rush Medical College became associated with the University of Illinois. In 1921 he became a member of the neurologic



JOHN FAVILL, M.D.

1886-1946

staff of Cook County Hospital. Here he served continuously until 1937, and during his last two terms was chief of the section. He also served as consultant to the Institute for Psychoanalysis and the Highland Park and Lake Forest Hospitals.

Dr. Favill took an active part in the various associations having to do with the fields he was interested in. In many of these associations he was honored with executive positions. He was president of the Chicago Neurological Society from 1926 to 1928, president of the Chicago Society for Personality Study from 1936 to 1937, president of the Central Neuropsychiatric Association in 1937-1938 and president of Medical Unit Commander's conference in 1937-1938. He held membership in the American College of Physicians, the American Neurological Association, the American Psychiatric Association and the Association for Research in Nervous and Mental Disease.

To the field of medicine he contributed three books, "Outline of the Cranial Nerves," 1933; "The Relationship of Eye Muscles to Semi-circular Canal Currents in Rotationally Induced Nystagmus," 1936, and "Outline of Spinal Nerves," 1946. In 1917 he published a memorial volume to his father, "Henry Baird Favill; Life, Tributes and Writings."

While neurology was his chosen field and he won recognition in it, his efforts were not confined to it. In 1924 he was commissioned major in the Army Reserve Medical Corps. With quiet and ceaseless effort he applied himself to the study of the problems of military medicine. He was promoted to the rank of lieutenant colonel in 1931 and to that of full colonel in 1938. From 1939 to 1942 he was Commanding Officer of United States General Hospital 114. In 1942, because of illness, he was placed on the inactive list.

His interest in mathematics led him into the study of navigation. In the September 1935 issue of the *Naval Institute Proceedings*, he published a new method for determining latitude. This gained for him the esteem of many old and seasoned navigators. Encouraged by this, he continued the study, and in 1940 he published "The Primer of Celestial Navigation." This book was to go through three editions and was a true contribution to the better understanding of the subject. It was used extensively in preparation of navigators during the last war. Not content with writing about navigation, he prepared himself, took the examination and won a certificate as navigator, United States Power Squadron. It is perhaps ironic that he suffered from seasickness and had no interest in sailing.

In the later years his search for knowledge took him more and more into the field of philosophy. At the time of his death he was compiling his contributions. He was interested in psychic research. While he had no brief for psychic cults, or for the idea of communications with the spirit world, to him the phenomenon of our awareness was still a mystery, and he believed that if one worked and studied the truth regarding it might sometime be recognized.

In relation to his nonmedical activities, he took membership in the American Society for Psychic Research, the American Legion, the Veterans of Foreign Wars, the Reserve Officers Association, the American Unitarian Association, the National Dairy Association, the Naval Institute and the United States Power Squadron.

He was a member of the University, the Saddle and Cycle, the Cliff Dwellers, the Wayfarers, the Army and Navy and the Commonwealth Club.

On June 20, 1917 John Favill was married to Rhea Statcup of New York city. This marriage was dissolved in 1934. He married Alice M. Wells on May 31, 1935. A daughter, Elaine, was born May 9, 1936.

Dr. Favill attended the Association for Research in Nervous and Mental Disease in December 1946, fully aware of the state of his health. He died of coronary thrombosis on Dec. 21, 1946, the day following his return.

The contributions made by Dr. Favill in his many fields of endeavor will speak for themselves and will reveal the quality of the man. The philosophy that guided and urged him on and the manner in which he carried out his ideas may be of greater interest. In his presidential address, "The Great Delusion," before the Central Neuropsychiatric Association, he exposed his philosophy and his confession of faith. He believed in Truth, not as something that one manufactures but as "some sort of a non-material reality." This truth had through the ages broken through to our awareness. Since this was the philosophy he believed in, then his "supreme function" was the recognition of Truth. To this end he must continually and persistently prepare himself. Not only did Dr. Favill believe in these concepts; his life bears out the fact that he carried them out. He must always master the details of any subject to which he turned his efforts. Not only must he learn the facts, but he must do everything he could to clarify them, so that they might be more simply stated and more easily perceived by others. His lectures were always revised, the nonessentials discarded and new facts added. His efforts in military medicine and in navigation were similarly characterized. He worked so quietly and unobserved that he almost got a reputation for being indolent. Quite the contrary, he was a ceaseless worker. Some of his work was conceived and planned when confined to bed. He always took his problems with him when on vacation. He utilized nearly every available hour to prepare himself for the "recognition of Truth." Bearing in mind his near worship of truth, one can understand his inherent distrust in any structure based on misconception, and also see why he had so much interest in mathematics. He always endeavored to reduce his problem to a mathematical equation, for there he felt secure in his reasoning. When discussing the

relationships of ocular muscles to the semicircular canal currents in rotationally induced nystagmus, he proved his thesis by an algebraic equation. Perhaps the work which brought him his greatest recognition was in the field of mathematics; namely, navigation. Interesting and characteristic of the man, it was not his love of the sea that gave him the impetus to study navigation; it was his love of facts and his struggle to prepare himself to recognize them. He will be remembered not only for what he did but for how he accomplished it.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

FUNCTIONAL CHANGES IN NERVE AND MUSCLE AFTER PARTIAL DENERVATION.

H. M. HINES, W. H. WEHRMACHER and J. D. THOMSON, *Am. J. Physiol.* **145**:48 (Nov.) 1945.

Hines, Wehrmacher and Thomson studied the effects of partial denervation on the gastrocnemius muscles of rats and cats. Partial denervation was obtained by section of the fourth and fifth spinal nerves in the rat and of the seventh lumbar nerve in the cat. At various times after partial denervation determinations were made of muscle weight and of isometric tension responses to direct stimulation and to stimulation of the tibial nerve. These determinations were controlled by observations on the contralateral (normal) extremities. Isometric tension responses were considerably decreased three days after partial denervation, but the tension responses nine, fourteen and fifty days after partial denervation were much more forceful than at the end of three days. This improvement in response was not considered the result of recovery from shock and trauma, nerve regeneration or recovery from weakness in the control extremity but was thought to result from hypertrophy of nondenervated muscle fibers and extension or unmasking of peripheral neuromuscular terminals.

FORSTER, Philadelphia.

AGE, SEX, CARBOHYDRATE, ADRENAL CORTEX AND OTHER FACTORS IN ANOXIA.

S. W. BRITTON and R. F. KLINE, *Am. J. Physiol.* **145**:190 (Dec.) 1945.

Britton and Kline studied the effects of low barometric pressures on experimental animals. Age, sex, species and environmental temperature were important factors in resistance to low barometric pressures. Rat fetuses and immature pouch opossums were highly resistant to anoxia. The high resistance declined rapidly in infant animals during the first one or two weeks after birth, and for a period the young animals were more susceptible than adults. The superior resistance of young animals may be due to the relatively large size of the adrenal glands, and the high glycogen content of the liver. Of the mammalian types studied, the American brown bat had the highest resistance. The female animals were more resistant to anoxia than the males. This, too, may be due to the relatively larger adrenal glands of females. The influence of the adrenal glands is further indicated by the absence of variation between the sexes in infancy, when the adrenal glands are of approximately equal size in the two sexes. The survival time under anoxia was inversely related to the environmental temperature. The resistance of rats to low barometric pressure was greatly augmented by the administration of carbohydrates, while the administration of insulin decreased tolerance to anoxia. Resistance to anoxia could be increased by inhalation of a mixture of carbon dioxide and oxygen and injection of dextrose solution. Exposure to anoxia did not alter serum levels of potassium, sodium and chloride. Britton and Kline conclude from their data that the adrenal cortex aids greatly in extending life under anoxic conditions.

FORSTER, Philadelphia.

FRACTIONATION OF LECITHINS AND CEPHALINS. E. A. WELCH, *J. Biol. Chem.* **161**:65, 1945.

The lecithins and cephalins are complex mixtures of chemical entities, differing from each other (a) in their component fatty acids; (b) in the case of the cephalins,

in the nitrogenous constituent, and (c) in the point of substitution of the phosphoric acid-base group in the molecule. A procedure is presented for the fractionation of the α and β isomeric forms of lecithin and cephalin. With use of this method, it was found that in brain the α forms predominate and in the heart and liver α -lecithin and β -cephalin predominate.

PAGE, Cleveland.

A METHOD FOR THE DETERMINATION OF DESOXYRIBONUCLEIC ACID, RIBONUCLEIC ACID, AND PHOSPHOPROTEINS IN ANIMAL TISSUES. G. SCHMIDT and S. J. THANNHAUSER, *J. Biol. Chem.* **161**:83, 1945.

The methods used at present for the determination of the higher nucleic acids in organs are based on certain color reactions of their carbohydrate components. The quantitative evaluation of these color tests gives satisfactory results with the free carbohydrates and with the purine nucleosides and nucleotides. Application of the color tests to the higher nucleic acids, however, encounters some serious difficulties, which arise mainly from the resistance of the pyrimidine nucleotides against hydrolyzing agents, from the instability of desoxyribose and from the necessity of separating the nucleic acid from the proteins. An extensive discussion of these problems has recently been given by Davidson and Waymouth. It occurred to Schmidt and Thannhauser that these difficulties might be avoided if the quantitative estimations of desoxyribonucleic acid and of ribonucleic acid could be based on phosphorus determinations rather than on color tests of their carbohydrate components. The prerequisite for such a method would be the possibility of separating quantitatively the phosphorus fraction of ribonucleic acid from that of desoxyribonucleic acid. The separation of both phosphorus fractions can be achieved by the selective destruction of ribonucleic acid under the influence of a mild treatment with alkali. Rat brain was found to contain 15.1 desoxyribonucleic acid and 32.6 ribonucleic acid, expressed as milligrams of phosphorus in 100 Gm. of fresh tissue. Negligible amounts of phosphoproteins were found.

PAGE, Cleveland.

OXYGEN POISONING: V. THE EFFECT OF HIGH OXYGEN PRESSURE UPON ENZYMES: SUCCINIC DEHYDROGENASE AND CYTOCHROME OXIDASE. W. C. STADIE and N. HAUGAARD, *J. Biol. Chem.* **161**:153, 1945.

Experiments on the effect of oxygen at high pressure on succinic dehydrogenase, cytochrome oxidase and cytochrome c are reported. Oxygen at 7 atmospheres inactivates the succinic dehydrogenase of rat liver, kidney or brain. The rate of inactivation, however, is relatively slow. The succinic dehydrogenase activity of brain tissue of rats killed by oxygen at 7 atmospheres is not different from that of normal animals. Cytochrome oxidase and cytochrome c are unaffected by oxygen at 7 atmospheres. The significance of these findings in the general problem of oxygen poisoning is discussed.

PAGE, Cleveland.

OXYGEN POISONING: VI. THE EFFECT OF HIGH OXYGEN PRESSURE UPON ENZYMES: PEPSIN, CATALASE, CHOLINESTERASE, AND CARBONIC ANHYDRASE. W. C. STADIE, B. C. RIGGS and N. HAUGAARD, *J. Biol. Chem.* **161**:175, 1945.

The enzymatic activities of preparations containing pepsin, catalase, cholinesterase and carbonic anhydrase were determined before and after exposure to oxygen at high pressure. No significant changes were observed. Cholinesterase is an example of a sulphydryl enzyme unaffected by oxygen.

PAGE, Cleveland.

OXYGEN POISONING: VIII. THE EFFECT OF HIGH OXYGEN PRESSURE ON ENZYMES: THE SYSTEM SYNTHESIZING ACETYLCHOLINE. W. C. STADIE, B. C. RIGGS and N. HAUGAARD, *J. Biol. Chem.* **161**:189, 1945.

The aerobic synthesis of acetylcholine by slices or homogenates of rat brain is unaffected by exposure to oxygen at high pressure. The choline acetylase activity of slices of rat brain is likewise unimpaired by excess oxygen. However, cell-free

preparations of acetylase are rapidly inactivated by oxygen. The relation of these findings to the problem of oxygen poisoning is discussed. PAGE, Cleveland.

ANAEROBIC GLYCOLYSIS IN NERVOUS TISSUE. M. F. UTTER, H. G. WOOD and J. M. REINER, J. Biol. Chem. **161**:197, 1945.

A method is described for the preparation from the central nervous system of cell-free extracts and homogenates exhibiting high rates of anaerobic glycolysis. A study of the variable factors in the preparation of the extracts and homogenates has been made. Active extracts and homogenates have been prepared from spinal cord, medulla, cerebellum and cerebrum. For complete activity these preparations need, in addition to glucose and buffers, adenosine triphosphate, hexose diphosphate, diphosphopyridine nucleotide, magnesium ions and nicotinamide. Evidence is presented that the "inhibitor" of brain extract reported by Geiger is a diphosphopyridine nucleotidase. Inhibition of the nucleotidase can be obtained with nicotinamide or by incubation of the preparation with diphosphopyridine nucleotide and bicarbonate buffer. Etherization of animals prior to preparation of glycolytic extracts and homogenates did not have any detectable effect on extracts and had slight or no effect on homogenates. The preparations have approximately linear activity with time and with increasing concentration of tissue for sixty minutes or longer. They, therefore, should prove useful in the assay of enzymes of anaerobic glycolysis of the central nervous system. PAGE, Cleveland.

PHOSPHORUS COMPOUNDS IN ANIMAL TISSUES: I. EXTRACTION AND ESTIMATION OF DESOXYPENTOSE NUCLEIC ACID AND OF PENTOSE NUCLEIC ACID. W. C. SCHNEIDER, J. Biol. Chem. **161**:293, 1945.

The pentose nucleic acid content of rat brain was found to be 184 mg. per hundred grams of wet tissue, while the desoxypentose nucleic acid was 124 mg.

PAGE, Cleveland.

ST. LOUIS ENCEPHALITIS VIRUS IN BLOOD OF EXPERIMENTALLY INOCULATED FOWLS AND MAMMALS. W. McD. HAMMON, W. C. REEVES and E. M. IZUMI, J. Exper. Med. **83**:175 (March) 1946.

Hammon and his collaborators state that of three species of mammals tested by peripheral inoculation (guinea pig, cat and horse) none showed viremia under conditions which suggested that any of these species would serve as a frequent source of mosquito infection. Of the birds tested (chicken, duck and dove) all showed viremia and might readily serve as natural sources of mosquito infection. Chickens were shown to be highly susceptible to infection with minute amounts of virus inoculated subcutaneously. Virus may appear in the blood of chickens within sixteen hours after inoculation, and it has persisted till at least the one hundred and twentieth hour. No fowl showed signs of illness as a result of the infection.

J. A. M. A.

LABORATORY TRANSMISSION OF JAPANESE B ENCEPHALITIS VIRUS BY SEVEN SPECIES (THREE GENERA) OF NORTH AMERICAN MOSQUITOS. W. C. REEVES, W. McD. HAMMON, G. G. WOLF and C. ESPANA, J. Exper. Med. **83**:185 (March) 1946.

Reeves, Hammon and associates tested 10 common species of western North American mosquitoes for their ability to act as vectors of Japanese B encephalitis virus. Of the 10 species of mosquitoes tested, 7 were demonstrated to be laboratory vectors. These 7 species represent three genera (*Culex*, *Aedes* and *Culiseta*). Transmission was made to mice twenty-one times and to a chicken once. These results, in addition to the published accounts by Japanese and Russian workers of

the natural epidemiology of this disease, led the authors to believe that this virus might well establish itself in North America, especially if introduced in areas where native encephalitides are now endemic. These studies also indicate that species of mosquitoes (*Culex tarsalis*, *Culex pipiens*, *Aedes dorsalis* and *Culiseta inornata*) now known to be fully incriminated vectors of the western equine or St. Louis encephalitis viruses can also serve as laboratory vectors of the Japanese B encephalitis virus.

J. A. M. A.

EXPERIMENTS ON CELL AND AXON ORIENTATION IN VITRO: THE ROLE OF COLLOIDAL EXUDATES IN TISSUE ORGANIZATION. PAUL WEISS, J. Exper. Zool. **100**:353 (Dec.) 1945.

About 5,000 tissue cultures of Schwann cells and nerve fibers in liquid or clotted mediums, with and without the inclusion of fibers of various kinds and dimensions (glass, textiles and synthetic resins, from 8 to 500 microns in diameter) were observed. Conclusions were reached concerning the mechanisms of adhesion, orientation, locomotion and association of spindle cells and axons in vitro.

A colloidal exudate given off by explanted tissue fragments slowly spreads centrifugally over all exposed surfaces and coats them with a fibrous mat ("ground mat"). The terminal processes of spindle cells and axons adhere to and follow the ground mat even in liquid mediums.

Orientation of the fibrils of the ground mat may be produced in both liquid and clotted mediums by placing the explant against a groove exerting strong capillary action or in contact with glass or textile fibers. Subsequent movement of the tissue will follow this linear course.

Even if the circumference of the cylinder is several thousand times the width of the cell processes, there is a longitudinal arrangement of the fibrils as the exudate moves down the cylinder. Cells and axons migrating along such a surface have longitudinal orientation.

Cells that have made contact with fibers of glass or synthetic resins embedded in a plasma clot seldom leave the fiber and move back into the clot. Cells advance more than twice as fast and as far along a glass fiber as they do inside the surrounding plasma clot. The many intersections of the fibrin framework of the clot account for the difference in rates of advancement. The differences in "regeneration rates" of nerve fibers can be explained on the basis of the organization of their surroundings (scar tissue or oriented tissue) rather than on differences in rates of intrinsic activity of the neurons concerned.

Favorable conditions for the aggregation of cells and the fasciculation of nerve fibers are created by liquid spaces, whether primary or produced by proteolysis.

The experiments have reconfirmed the principle of "contact guidance" of spindle cells and nerve fibers and have shed light on the mechanisms of "thigmotaxis," or "stereotropism," in tissue formation. The morphogenic significance of fibrous exudates in development and wound healing has received wider support.

REID, Boston.

THE NERVOUS SYSTEM AND REGENERATION OF THE FORELIMB OF ADULT TRITURUS: IV. THE STIMULATING ACTION OF A REGENERATED MOTOR SUPPLY. MARCUS SINGER, J. Exper. Zool. **101**:221 (March) 1946.

Experiments were designed to isolate a regenerated motor supply and then to observe its influence on growth of the amputated limb. The results show that, although the normal isolated motor supply of a limb is incapable of supplying the neural influence necessary for regeneration of the limb, the neural requirements can be met by a regenerated complement of motor fibers. The observations suggested that a number of motor elements greater than the normal, as brought about during the course of motor reinvasion, is the important factor.

Since the neural factor essential for regeneration of the limb may be motor as well as sensory, Singer suggests that such neural activity is common to all nerve fibers.

REID, Boston.

SUSCEPTIBILITY TO POLIOMYELITIS. C. ARMSTRONG and D. J. DAVIS, *Pub. Health Rep.* 60:710 (June 22) 1945.

Persons exposed to poliomyelitis may react quite differently, some having constitutional symptoms with paralysis while others harbor the virus but show no symptoms. The reason for this difference is unknown, as is the actual reason for the common occurrence of virus-neutralizing antibodies in serums collected from the general population. Approximately 70 per cent of patients with poliomyelitis form antibodies slowly, if at all, after a recognizable attack. If this neutralizing property is an inherited characteristic, it is possible that the fathers and mothers of patients with the paralytic form of poliomyelitis might be found to show a higher incidence of non-neutralizing serums than would persons of corresponding age from the general population. The serums for a determination of this point were collected from 42 mothers and 27 fathers of hospitalized patients with paralytic poliomyelitis in North Carolina during the 1944 outbreak. When tested with the Lansing strain of poliomyelitis virus in white mice, the serums from 39 mothers neutralized the virus, 3 partially neutralized it and none had no neutralizing action. Of serums from 27 fathers, 23 neutralized it, 3 partially neutralized it and 1 had no neutralizing action. These results give no indication that paralytic poliomyelitis is more likely to occur among those whose parents do not readily produce circulating antibodies against the virus.

J. A. M. A.

CAROTID SINUS AND RETINAL CIRCULATION. RISER and others, *Presse méd.* 53:161 (March 31) 1945.

Riser and his associates report observations on 50 subjects in whom they determined simultaneously the retinal arterial tension and the general arterial tension while performing various manipulations on the carotid sinus, such as digital compression of the sinus region, inhibition of the sinus by procaine hydrochloride and compression of the carotid artery below the sinus. They stress that the variations provoked in the general and in the retinal arterial tension by excitation of the carotid sinus are always synchronous and of the same amplitude. There never appeared a direct action of the sinus on the retinal circulation that could be separated from the action on the general circulation.

J. A. M. A.

ELECTROPHYSIOLOGIC STUDIES ON METRAZOL EPILEPSY. P. CHAUCHARD and others, *Presse méd.* 53:201 (April 21) 1945.

Chauchard and his associates found in experiments on rabbits, guinea pigs and rats that metrazol injections result in an inverse modification of the excitation time of the cerebral cortex (prolongation) and the peripheral nerves (shortening). The effects of metrazol on the nervous centers are complex. The investigations conducted by the authors confirm earlier observations which attribute to the base of the brain an important part of the metrazol attack, but they go further and bring proof that the cerebral cortex, far from being stimulated by metrazol, is depressed by it. This is in accord with the fact that in man the attack is accompanied by loss of consciousness, that is, by suppression of the cortical function. In the encephalogram, under the influence of metrazol the augmentation of voltage is on a par with a retardation of the waves, which speaks in favor of a depression. The authors show that the complex action of metrazol, depressing the superior centers and stimulating the inferior ones, must not be confounded with that of ordinary stimulants, such as strychnine, which excite the brain and the lower centers simultaneously. Great similarity exists in metrazol epilepsy, insulin coma and electric shock, which are used in psychiatry.

J. A. M. A.

Neuropathology

PROTOZOAN PARASITE OF CENTRAL NERVOUS SYSTEM. N. VEERARAGHAVAN, *Indian J. M. Research* 32:207 (Oct.) 1944.

Veeraraghavan encountered forms in the midbrain of guinea pigs experimentally infected with rabies which have not apparently been previously described.

The peculiar forms have been investigated over the past six years. The conclusion was reached that they are due to the presence of a parasite, probably protozoal in character, which is specific to the central nervous system. It has not been possible to identify this parasite with any previously described, such as *Encephalitozoon cuniculi*, or with any known species of *Toxoplasma*. The protozoal parasite was first encountered in the midbrain of guinea pigs infected with the jackal strain of rabies virus. The parasite, with the exception of certain cystic forms of doubtful significance, invariably occurred in the cytoplasm of nerve cells, particularly those ventral to the central canal of the midbrain. In a few cases, parasites were observed also in the Purkinje cells of the cerebellum and in the hippocampus major. The smallest forms of the parasite encountered were minute "spores." They were regularly seen in the midbrain of the naturally infected dogs and jackals and in the brains of guinea pigs inoculated with suspensions of their brains. The next stage of the parasite appeared to be the "ring" form. It might be round or oval, and it was variable in its position within the vacuole. Certain forms resembling the *accolé* forms of the malaria parasite were occasionally noted. These consisted of a crescentic bridge of cytoplasm with a rounded chromatin dot. In slightly older forms the chromatin mass was slightly larger, the protoplasm was thickened and the parasite assumed a variety of shapes. Segmentation of the chromatin appeared to be the next stage in the development of the parasite. In the segmenting forms the protoplasm appeared to be a solid mass with a varying number of chromatin dots. No evidence was found to suggest that the various forms of the parasite were the result of alterations in the constituents of nerve cells. The possibility of the parasite being a natural infective organism common to dogs and jackals, and unconnected with rabies infection, was investigated. Neither parasites nor Negri bodies were ever encountered in animals without rabies. Certain stages in the life cycle of the protozoal parasite described appear to be "filtrable"; it has been possible to produce evidence of infection in experimental animals by the inoculation of suspensions of brain passed through Berkefeld V and N candles. The protozoal parasite appears to be specific to the central nervous system, and in spite of exhaustive searches it has never been observed in other organs and tissues. It was not observed except in association with natural or experimental rabies. The suggestion has been put forward that Negri bodies may represent a stage in the life cycle of the parasite.

J. A. M. A.

DYSTONIA MUSCULORUM PROGRESSIVA (TORSION DYSTONIA). C. DE LANGE, *Ann. pædiat.* **164**:169 (April) 1945.

Cornelia de Lange made microscopic studies of the brain, the greater part of the spinal cord and the visceral organs of a Jewish man who died at 45 and in whom the disorder began at the age of 8. The diagnosis of dystonia musculorum progressiva was verified by competent neurologists. The corpus striatum proved practically normal, but various parts of the brain and the cord presented anomalies which doubtless had a degenerative anlage. The author is of the opinion that in the cases of dystonia of idiopathic or degenerative type there exist no specific anatomic changes but that the disorder is the result of a disturbance in the dynamics of the brain, spinal cord, nerves and muscles. The basis of this disturbance might be a metabolic process which produces no changes that are microscopically demonstrable.

J. A. M. A.

Psychiatry and Psychopathology

SENILE PSYCHOSIS AND PELLAGRA. H. A. MEYERSBURG, *New England J. Med.* **233**:173 (Aug. 9) 1943.

Meyersberg says that several patients with psychoses of the senile type have been observed to improve after therapy with nicotinic acid, thiamine, riboflavin and substances rich in the vitamin B complex. Review of their records has shown that 2 had atypical pellagra. In the first patient, a woman aged 55, the late mani-

festations were like those of a vascular disturbance, although the earlier ones were neurasthenic. The latter disturbances, the memory defects and the confabulatory episodes resembled the Korsakoff syndrome, which may occur either in the senile psychoses or in pellagra. The episodes of stupor were similar to those described in pellagrins. The cutaneous lesions were those of riboflavin deficiency, and the mucosal alterations were the combined effect of several deficiencies. The response to treatment puts this case definitely in the pellagra group. The effect of nutritional inadequacy in a patient with a subclinical encephalopathy of the combined senile and vascular type was illustrated by the second patient, a man aged 78. The reestablishment of adequate neurologic function and the concurrent disappearance of the somatic signs of deficiency under therapy indicate that the neuropsychiatric dysfunction was related to biochemical imbalance. The neuropsychiatric manifestations of pellagra usually appear after dermal, oral or gastrointestinal manifestations have developed. In a small proportion of cases, however, neuropsychiatric signs alone are manifest. The senile pellagrous type of encephalopathy may respond well to treatment with crystalline vitamin B products or with natural vitamin B concentrates. The recognition of this group of cases may permit effective therapy. The maintenance of an optimal dietary by the normal aged person, as well as by the senile invalid, is of primary importance.

J. A. M. A.

EFFECTS OF ENCEPHALITIS OCCURRING DURING CHILDHOOD ON BEHAVIOR AND PERSONALITY: STUDY OF 50 CASES. J. V. GREENEBAUM, L. A. LURIE, B. LEICHTENTRITT and FLORENCE M. ROSENTHAL, Ohio State M. J. **41**:1018 (Nov.) 1945.

Greenebaum and his associates report observations on 50 children who were referred to the Child Guidance Home because of behavior disorders and personality difficulties which were causally related to a previous attack of encephalitis. The patients were followed for from three to twenty-five years. The fact that there were 39 males and 11 females seems to indicate that males are more susceptible to disorders of this type than are females. The onset of the disease was predominantly early in infancy, in the majority of cases occurring before the age of 5 years. The onset of the behavior problems and personality changes occurred mostly below the age of 10 years. In the majority of the children the behavior and personality difficulties appeared immediately after the onset of the disease. The virus type of encephalitis predominated in this series. Neurologic abnormalities (pyramidal, extrapyramidal, ocular) were present in all but 9 patients. Five had grand mal, 2 petit mal and 4 paralysis agitans. The range in intelligence quotients was from 51 to 118. Only 14 were feeble-minded. Of 20 children who were retested, 9 showed no change in the intelligence quotient, 1 showed improvement and 10 were deteriorated. The children fall into three categories: those with behavior difficulties, the psychopathic and the psychotic. Only 9 of the 50 patients are at present adjusted.

J. A. M. A.

Meninges and Blood Vessels

TORULA HISTOLYTICA (CRYPTOCOCCUS HOMINIS) MENINGITIS. STEWART H. JONES and GUSTAVUS H. KLINCK JR., Ann. Int. Med. **22**:736 (May) 1945.

Jones and Klinck report their observations on a man aged 50 who had meningitis caused by *Torula histolytica*.

Despite supportive treatment, which consisted of blood transfusions and the oral and intravenous administration of iodides and sulfadiazine, no improvement occurred. The patient was given gentian violet medicinally intravenously and thymol intramuscularly. No benefit followed the use of either substance. Penicillin was unobtainable in sufficient quantity for adequate therapy. In spite of all efforts, the patient died.

Postmortem examination confirmed the diagnosis of torular infection, which involved the brain, the spinal cord and the kidneys.

In vitro experiments were performed, and sodium sulfadiazine and penicillin showed the greatest growth-inhibiting power. The experiments failed to show any therapeutic value of sodium sulfadiazine in experimental infections in mice.

GUTTMAN, Philadelphia.

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: REVIEW OF EXPERIENCES SINCE INTRODUCTION OF SULFONAMIDE THERAPY; IV. PNEUMOCOCCUS MENINGITIS. A. F. HARTMANN, FRANCES M. LOVE, DOROTHY WOLFF and BARBARA S. KENDALL, *J. Pediat.* 27:115 (Aug.) 1945.

Hartmann and his associates review the clinical, laboratory and postmortem studies of all patients with pneumococcal meningitis admitted to the St. Louis Children's Hospital from the time the first sulfonamide drug was available for treatment (December 1936) to Nov. 1, 1944. The following conclusions have been reached: Apparently, any type of pneumococcus may cause meningitis. The pathway by which the pneumococcus may gain entrance to the meninges and spinal fluid varies and should, whenever possible, be established because of its possible surgical implications. The incidence of "surgical" mastoiditis as a portal of entry is much greater than with meningococcal infections, but also apparently much smaller than with hemolytic streptococcus infections. When the temporal bone is involved, there seems to be a characteristic pathologic picture which includes (1) a high incidence of purulent labyrinthitis; (2) the formation of "empyemic membrane"; (3) peculiar organization of bubbly exudate, which leads to pseudogland formation, and (4) a high incidence of bilateral involvement. A diagnosis of pneumococcal meningitis can be made with certainty only by lumbar puncture and proper examination of the spinal fluid. The great value of early diagnosis far outweighs any theoretic danger imposed by lumbar puncture. Treatment should be started as early as possible with penicillin and a sulfonamide drug in high dosage. Mortality seems more related to delayed diagnosis and institution of intensive therapy than to any other single factor. Sequelae, such as hydrocephalus, epilepsy and mental retardation, may be expected, especially when the infection occurs during infancy and is not eradicated immediately.

J. A. M. A.

MIDDLE MENINGEAL HEMORRHAGE. R. ORGIAS, *New Zealand M. J.* 44:242 (Oct.) 1945.

Orgias describes 7 cases of middle meningeal hemorrhage which were encountered among 1,529 cases of head injury. Of the 67 deaths from head injury, 3 were due to middle meningeal hemorrhage. A detailed inquiry into the circumstances of the accident and the condition of the patient are of great importance for a correct diagnosis. The most useful sign in these cases was coma or a deepening coma or a drift into unconsciousness. The pupil was dilated or had become dilated on the affected side in all cases. The reaction to light was variable, being usually depressed or absent. The pulse was full, and the rate was between 50 and 60. The blood pressure was moderately elevated. There was usually some increase in tone of the limbs or loss of movement on the contralateral side. An inspection of the head with palpation is important, as this may reveal bruising or edema on the side of the lesion. There is usually a fracture across the line of the middle meningeal artery. In certain instances without a history of injury the diagnosis can only be suspected and an exploratory trephine is necessary. Operation should not be delayed. None of the patients showed a dramatic return of consciousness. Therefore efforts had to be directed toward preventing pulmonary complications and maintaining nutrition. The foot of the bed was raised and the patient nursed on the side and rolled to the opposite side hourly. A special nurse kept the airway clear with suction. Three pints (1.5 liters) of nutrient fluid containing 1,500 calories was given by stomach tube daily. The hemoglobin was restored to normal

as soon as possible by blood transfusion to insure adequate oxygenation of the brain. Sulfadiazine, 4 Gm. daily given by stomach tube, helped to control pulmonary infection. All patients were given $\frac{1}{2}$ grain (32 mg.) of phenobarbital twice daily for several months in the hope that traumatic epilepsy could be avoided.

J. A. M. A.

TUBERCULOUS MENINGITIS IN INFANT VACCINATED WITH BCG VACCINE. R. GORLERO BACIGALUPI, Arch. de pediat. d. Uruguay **16**:545 (Sept.) 1945.

Gorlero Bacigalupi reports that an infant who had received BCG vaccine within the first three days after birth, and whose parents and family were normal, developed normally up to 22 months of age, when he became ill with acute tuberculous meningitis and died three days later. The diagnosis was confirmed by cultures of the cerebrospinal fluid and by inoculation of the cerebrospinal fluid into guinea pigs. There was a history of contact of the infant with a tuberculous neighbor when he was 8 months old.

J. A. M. A.

Diseases of the Brain

SUBACUTE BACTERIAL ENDOCARDITIS WITH CEREBRAL EMBOLISM SUCCESSFULLY TREATED WITH PENICILLIN AND HEPARIN. E. T. GREEN, Canad. M. A. J. **53**:425 (Nov.) 1945.

Green reports that after the detection of *Streptococcus viridans* in three blood cultures, taken on successive days, of a woman aged 25, who first came under observation because of cerebral embolism, penicillin and heparin were given over ten days until a total of 1,200,000 units of penicillin and 200 cc. of heparin had been administered. One week after completion of the course of treatment the patient was sitting out of bed and six days later was allowed to go home. The treatment seems to have had a favorable influence in recovery from the effects of the embolism.

J. A. M. A.

TOXOPLASMIC ENCEPHALITIS. R. S. DOW, Northwest Med. **44**:382 (Dec.) 1945.

Dow presents the histories of 2 patients with toxoplasmic encephalitis. The first was a child aged 2 who exhibited all the clinical manifestations of toxoplasmic encephalitis. These included: (1) healed or inactive chorioretinitis; (2) reduced vision; (3) strabismus, nystagmus and microphthalmos; (4) intracerebral calcification; (5) convulsive seizure (1); (6) internal hydrocephalus from a block at the aqueduct of Sylvius; (7) retarded speech development, and (8) mental deficiency. The case was complicated by the presence of postoperative meningitis and wound infection due to *Staphylococcus aureus*. The serologic tests for *Toxoplasma* had not been done, and attempts to infect laboratory animals with spinal fluid were unsuccessful. The second patient, a girl aged 5, exhibited many of the signs and symptoms of toxoplasmic encephalitis. Treatment with sulfapyridine was tried and continued for ten days, a blood level of 5 to 10 mg. per hundred cubic centimeters being maintained. She seemed much improved for three weeks; then seizures recurred. This observation and the results obtained in laboratory animals make it desirable to continue the use of sulfonamide compounds whenever a diagnosis of toxoplasmic encephalitis is made and when there has not been extensive permanent cerebral damage. It is felt that the condition is more common than the reported cases would indicate and that a greater incidence will be found when knowledge of this disorder has become more generally available.

J. A. M. A.

BLAST INJURY OF BRAIN. L. ROGERS, M. J. Australia **2**:209 (Aug. 18) 1945.

Rogers states that structural changes may be produced in the brain or cord of those in the vicinity of an explosion. He reports that a seaman aged 19, after

standing close to a 4 inch (10 mm.) gun during its discharge, noticed a sudden numbness in the left hand and arm, which lasted about ten minutes. Three weeks later began the first of a series of attacks of numbness and tingling, which, starting in the left hand, spread to the elbow, shoulder and side of the face and were accompanied by involuntary abduction and elevation of the arm, spasm of the face and loss of consciousness for a few minutes. On recovery there was some residual weakness of the left upper extremity, which gradually increased and spread to the leg, and seizures became more frequent, occurring four to six times a day. It was decided to explore the postcentral areas, and a bone flap was turned down in this region. The dura in the posterior part of the field was bulging, and when it was opened the cerebral gyri here were seen to be green, widened and elevated over an area about the size of a penny. Incision of the brain in this area revealed a shallow but extensive cavity containing old blood clot. This was removed, and the patient made an uninterrupted recovery; some residual weakness and astereognosis remained. Somewhat similar cases were reported by Mott in World War I, the lesions being discovered at necropsy. It has been suggested that the mechanism responsible for the production of the cerebral lesions is the hydraulic-like pressure transmitted to the cerebrospinal axis in its closed bony walls by sudden compression of the thoracic cage. Such compression must produce violent back pressure on the venous side of the circulation. A sudden rupture of vessel walls may conceivably be caused by the decompression which suddenly succeeds the compression wave.

J. A. M. A.

IMPORTANCE AND VALUE OF ELECTROENCEPHALOGRAPHY IN CRANIOCEREBRAL INJURIES. PUECH, FISCHGOLD, VERDEAUX and BRUN, *Presse méd.* 53:547 (Oct. 13) 1945.

According to Puech and his co-workers, a patient with a recent injury and with normal electroencephalograms, or with a slight deviation from normal, will, as a rule, recover rapidly and without surgical intervention provided the alpha rhythm is preserved. A patient with an old injury and with abnormal electroencephalographic tracings after coma has subsided presents a serious problem. Deviation from normal may be caused by hematoma, cerebral edema or hypotension. A recent fracture of the cranium, with concussion and laceration of the brain, may cause slight deviation from normal. The electroencephalographic studies should be made as soon as possible after injury and should be repeated as often as possible, waves from various cerebral areas being recorded simultaneously. Thus, the tracings can aid in ascertaining an improvement in the primary lesion and clarify the situation without resort to operation. In children an injury will cause more deviation from normal than a lesion of the same degree in adults. Considerable deviations at the level of the frontal lobes should not be regarded too seriously. Preventive treatment for epilepsy with sedatives is indicated in cases in which definite deviation from normal continues for a prolonged period after injury. Electroencephalograms and the clinical course were followed for one to ten years after craniocerebral trauma in 15 cases. The tracings showed abnormalities in 9 cases but were normal in the remaining 6. Electroencephalograms can reveal the existence of severe trauma in the past and of a persisting cerebral lesion, but the occasional absence of electroencephalographic abnormality does not exclude the existence of a cerebral lesion.

J. A. M. A.

CEREBRAL METASTASES OF OVARIAN STRUMA. L. DE BAKAY JR. and T. DE LEHOCZKY, *Confinia neurol.* 6:22, 1944.

Cerebral metastases of ovarian struma in a woman aged 57 were observed by de Bakay and de Lehoczy. A dermoid containing thyroid tissue was removed from the ovary of the patient. Six to eight years after this operation there appeared indistinct symptoms, such as fatigue and a slight disturbance in gait; later, hyperthyreosis and signs of a supratentorial neoplasm appeared. Mental disturbances

appeared at the same time. Gradually developing left hemiparesis and bilateral papilledema with punctiform hemorrhages were observed, in the absence of sensory disturbance. These symptoms suggested a frontoparietal tumor on the right side. When ventriculographic study was attempted, two incisions in the occipital region revealed a small neoplasm, in the occipital bone. It consisted of thyroid tissue and was considered a metastasis of the previous ovarian struma. This concept was supported by the identical microscopic structure of the ovarian struma and the bone tumor. The case differed from instances presenting the usual syndrome of metastatic brain tumor in that bilateral symptoms referable to the pyramidal tract and impairment of consciousness were observed as late as two weeks prior to death. It is probable that there was another tumor in the right frontoparietal region, a metastasis similar to that in the occipital bone.

J. A. M. A.

CEREBRAL COMPLICATIONS OF RENAL DISEASES IN CHILDREN. C. PAVEZ, *Rev. chilena de pediat.* **16**:1082 (Nov.) 1945.

According to Pavez, the most important neurologic symptoms of progressive chronic nephritis with hypertension in children are those indicating intracranial hypertension (acute headache, acute meningeal symptoms and either visual disorders or amaurosis). The neurologic symptoms subside with the improvement of the renal lesion, if the latter responds favorably to proper therapy. The differential diagnosis between nephritis and meningitis or cerebral tumor is of importance. The prognosis depends on the course of the renal disease. Two cases of children aged 10 and 13 years, respectively, are reported.

J. A. M. A.

TREATMENT OF BILATERAL ACOUSTIC TUMORS: REPORT OF SIX SURGICAL CASES, WITH REVIEW OF THIRTEEN CASES FROM LITERATURE. R. FRYKHOLM, *Acta chir. Scandinav.* **92**:451 (Oct. 5) 1945.

Frykholm reports 6 cases of bilateral acoustic tumors in 3 men and 3 women, 5 of them between the ages of 20 to 28 and the sixth a woman aged 44. All the patients received surgical treatment; 1 of them died during the operation, and 2 others showed no improvement and survived only one to two months. The 3 remaining patients were relieved from most of their distressing subjective symptoms and showed improvement in their work capacity. One of them has survived the bilateral intracapsular enucleation of the tumors for more than seventeen years. In the 2 patients on whom surgical intervention was carried out early, the treatment resulted in definite benefit. Cases of general neurofibromatosis in which the lesions are widely distributed within the central and peripheral nervous systems, with the severe alterations not due to the acoustic tumors, should be excluded from surgical treatment. In all cases a bilateral exposure of the cerebellum should be performed. The dura should not be sutured when the wound is closed unless both tumors have been radically removed. If some hearing function is preserved, the tumor on the side on which loss of hearing is most advanced should be attacked first and removed as radically as possible, preferably with preservation of the facial nerve. The patient will probably not improve completely, but he will certainly be in a better condition than if he were totally deaf. The other tumor is not attacked until the general condition begins to deteriorate or loss of hearing is complete. If improvement is not attained by the unilateral extirpation and if the patient's condition is desperate, the other tumor may be extirpated in a second session without regard to hearing function but with care to avoid bilateral facial paralysis. If the patient is already completely deaf, both tumors should be removed as radically as possible. This can be performed in one or two stages, depending on how well the operation is tolerated. If the facial nerve has been preserved during the removal of one tumor, a radical extirpation may be attempted on the opposite side; otherwise only an intracapsular enucleation is performed.

J. A. M. A.

Peripheral and Cranial Nerves

CAUSALGIA SECONDARY TO INJURY OF MAJOR PERIPHERAL NERVES: TREATMENT BY SYMPATHECTOMY. F. F. ALLBRITTEN JR. and G. L. MALTBY, Surgery 19:407 (March) 1946.

Patients suffering from causalgia continue to be admitted to hospitals with a diagnosis of severe psychoneurosis, and prolonged delay in treatment is a usual occurrence. During this period of delay the changes of disuse affect the extremity. This is of particularly serious import when the hand is involved. Despite the lack of an adequate etiologic explanation of the pain, interruption of the sympathetic nerve supply to the extremity greatly modifies or abolishes the symptoms of the disease. During the twelve months preceding this report, 67 patients were admitted to the hospital with which the authors are associated with injury to a major peripheral nerve and causalgia of sufficient severity to warrant treatment. The seat of the maximum pain was in the distribution of the posterior tibial nerve or of the median nerve. Thirty of this group desired sympathectomy after experiencing relief from sympathetic block. Of this group, 22 had lumbar sympathectomies and 8 had section of the dorsal preganglionic fibers. Good to excellent results were obtained in 28 of the patients. Sympathectomy failed to relieve symptoms and reestablish use of the affected part in 2 patients. The sympathectomy should be of sufficient extent to include the area of injury as well as the area of symptoms. Early sympathectomy will in the vast majority of cases relieve the symptoms of the disease and prevent the profound disabilities of disuse.

J. A. M. A.

CONGENITAL MALFORMATIONS OF FIRST THORACIC RIB: CAUSE OF BRACHIAL NEURALGIA WHICH SIMULATES CERVICAL RIB SYNDROME. J. C. WHITE, M. H. POPPEL and R. ADAMS, Surg., Gynec. & Obst. 81:643 (Dec.) 1945.

White and his associates report 10 new cases of congenital abnormality of the first thoracic rib. In 5 of these cases operation has been performed for relief of specific complaints, while in 5 others the condition has remained wholly asymptomatic. Malformations of the first rib generally consist of a rudimentary structure terminating in a synostosis or pseudoarthrosis with the second rib near the scalene tubercle or in a free end in the soft tissues at the base of the neck, which may be connected by a ligamentous band with the manubrium sterni. On rare occasions the first rib may have a joint near its lateral angle before it fuses with the second rib. Other skeletal abnormalities which are frequently present and which cause distortion of the thoracic outlet consist in deformities of the second rib and of the upper end of the sternum, scoliosis of the cervicothoracic portion of the spine and vertebral anomalies. Symptoms and clinical evidence of an abnormal first rib consist in supraclavicular bony prominence, irritation or paralysis of the brachial plexus and compression of the subclavian vessels as they cross the defective rib. Cervical arthritis, early carcinoma of the thoracic apex and herniation of a lower cervical intervertebral disk must be considered in the differential diagnosis of brachial neuralgia, even in the presence of an anomalous rib. Malformation of the first thoracic rib cannot be differentiated clinically from cervical rib. It can be accurately diagnosed in an anteroposterior roentgenogram which includes all the cervical and the uppermost thoracic vertebrae, provided the picture is taken with a long exposure and the mandible in motion. A considerable proportion of deformities of the first rib are large enough to cause mechanical compression of the nerves and vessels at the thoracic outlet. When symptoms are attributable to this condition, conservative orthopedic measures should be tried before surgical intervention. Scaleneotomy alone rarely suffices to decompress these structures but must usually be accompanied by radical resection of the rib from a point close to its articulation with the transverse process forward to its attachment to the second rib or where it disappears beneath the clavicle.

J. A. M. A.

DENERVATION AND RE-INNervation OF HUMAN VOLUNTARY MUSCLE. R. E. M. BOWDEN and E. GUTTMAN, *Brain* 67:273, 1944.

Bowden and Guttman made biopsies of 140 specimens of muscle from 86 cases of peripheral nerve injuries and studied the innervation, denervation and reinnervation of human muscle in this material. Denervation produces progressive and ultimate shrinkage of the muscle fibers. Up to three years after denervation no degeneration or disruption of muscle fibers is observed, but shrinkage of fibers and increase of connective tissue may be so advanced that reinnervation does not produce a well functioning unit. The essential changes during this three year period are progressive, but unequal, shrinkage of muscle fibers, progressive depletion of the sarcoplasm of the end plate, progressive distortion of the pattern of innervation and vascularization. After this interval disruptive changes occur, and longitudinal splitting of muscle fibers together with shrinkage takes place. Fragments of myofibrils become embedded in connective tissue, and in the latest stages muscle fibers may be represented by tubes filled with pyknotic nuclei and granules or fragments of muscle tissue. The pattern of innervation is intact for three months after denervation. After this the end plates become increasingly difficult to identify, and the pattern of innervation is distorted by the proliferating connective tissue. Permeability of the vessels is increased soon after denervation. The walls of the vessels then become thickened and the capillary bed is reduced. In the latest stages of denervation muscle is represented by fat, connective tissue, vessels and the larger empty nerve trunks. Within three years the changes in the muscle may be reversed to some extent by reinnervation. After three years it is questionable whether useful recovery is possible.

Bowden and Guttman conclude that biopsy of muscle is a useful aid in the diagnosis, prognosis and treatment of peripheral nerve injuries. Biopsy observations must be evaluated with respect to the state of the muscle and the nerve and the period of reinnervation. Different types of lesions of the nerve trunk produce characteristic patterns of reinnervation, and thus it is possible to differentiate neurotmesis, axonotmesis, partial lesions and such entities as traction injuries, unaided unions and unsuccessful sutures. After axonotmesis the rate of growth of axon tips is probably not greater than 3 mm. per day. Biopsy observations must be considered in connection with full clinical data. The limitations of the biopsy method are as follows: (1) The biopsy specimen may contain no nerve fibers; (2) the smallness of the specimen may involve error, and (3) the necessary period of waiting for reinnervation before biopsy may not be justified.

FORSTER, Philadelphia.

TRAUMATIC INJURIES OF PERIPHERAL NERVES: I. SIMPLE COMPRESSION INJURIES OF THE RADIAL NERVE. SYDNEY SUNDERLAND, *Brain* 68:56, 1945.

In order to determine the course of regeneration in cases of simple compression lesions of the radial nerve, Sunderland observed 7 patients, 5 of whom presented compression of the nerve in sleep, 1 had compression due to faulty use of crutches and 1 had been pinned beneath a truck. Restoration of function was determined by return of full range and power of movements. Wasting of muscles was determined by measurements of the arms at fixed points. Some variation in the degree of motor involvement was present. Sunderland observed that electrical excitability and sensation were not impaired to the same extent as was motor power. The escape of sensory fibers from the compression is attributed to a combination of factors, including anatomic arrangement of fibers, differential susceptibility of different types of fibers and perhaps other biochemical or morphologic properties. Sensory defects appear with the more severe injuries and indicate that restoration of motor function will be delayed. Muscular wasting occurred in 5 of the 7 cases. This is assumed to be due to early and rapid restoration of function. A normal nerve may be involved during sleep if the compression is sufficiently severe and prolonged. In all instances recovery was spontaneous and

in 5 cases occurred three to four months after injury. The course of recovery in cases of nerve compression differs from that in cases of nerve division and resuture in the following ways: (1) Spontaneous reappearance of function following compression occurs in from fifteen to more than sixty-one days; (2) recovery appears simultaneously in muscles in which lengths of the nerve fiber vary; (3) there is no orderly progress of regeneration; (4) two or more muscles may begin simultaneously to contract again, and once conduction reappears in one muscle a short interval elapses before all muscles supplied by the nerve are contracting; (5) the site of the first appearance of recovery varies, and more distally supplied muscles may recover first; (6) the time of appearance of motor function and the time required to recover power completely in the various muscles are in no way related to the length of the nerve fibers.

Sunderland concludes from these observations that the histopathologic changes leading to interruption of conduction after simple compression injuries differ from those occurring after anatomic interruption of the nerve fibers and that these changes are reversible and do not involve wallerian degeneration.

FORSTER, Philadelphia.

LESIONS OF THE NERVOUS SYSTEM ASSOCIATED WITH POLYRADICULONEURITIS. D. NIETO, *Bol. lab. de estud. med. y biol.* 1:261 (Dec.) 1942.

Nieto reports anatomic studies in 2 cases of polyradiculoneuritis. A man aged 42 was admitted to a hospital for mental disease with a clinical picture of an exogenous psychosis, probably alcoholic. The period of confusion cleared up after eleven days at the hospital. Two weeks later polyneuritis began to develop. There were pronounced motor changes and less severe impairment of sensation. The patient died of pneumonia two months after the onset of the polyneuritis. There was no fever during the course of the disease. The spinal fluid showed 11 cells per cubic millimeter, with 200 mg. of albumin per hundred cubic centimeters. In the second case the clinical diagnosis was poliomyelitis. Histologic examination in this case showed a condition very similar to the first. The author believes that he is justified in considering that these patients had the same disease.

Macroscopic examination of the spinal cord and spinal meninges showed nothing significant. Microscopic examination of the spinal cord showed diffuse lesions in the anterior horns, which were evidently secondary to involvement of the roots and peripheral nerves. The histologic picture was that of retrograde degeneration. There was no evidence of perivascular infiltration within the cord and no cellular response in the meninges. There was no increase in microglia cells; a mild reaction of the oligodendroglia was noted.

The roots and nerve trunks were slightly swollen. Microscopic examination of the roots and peripheral nerves showed some congestion, with dilated vessels; rare small hemorrhages, and occasional perivascular infiltration. There was pronounced degeneration of the axis-cylinders and myelin sheaths.

The author doubts whether an inflammatory process could have been the cause of such extensive changes in the roots and nerve trunks without some meningeal infiltration. He thinks that the inflammatory reaction within the peripheral nerves and roots was probably secondary to degeneration of the nerves. As a result of his histologic observations in these 2 cases, he is inclined to believe that the pathologic process was due to action on the nerves of a toxic agent.

N. SAVITSKY, New York.

NEUROGRAPHIA. A. ASENJO, M. CONTRERAS and C. VILLAVICENCIO, *Rev. de psiquiat.* 10:54, 1945.

The authors report 2 cases in which the precise site of injury to peripheral nerves was demonstrated by the injection of iodized poppyseed oil into and around

the nerve. Saito, in 1933, suggested the intraneural and perineural injection of a colloidal suspension of thorium dioxide. The authors used iodized poppyseed oil because the thorium dioxide caused rather pronounced connective tissue reactions. The amount of iodized oil injected varied with the thickness of the nerve (from 0.5 to 2 cc.). About one-fourth the amount was injected into the perineural region and the rest into the nerve itself. No harmful effects from the injection of iodized poppyseed oil were observed in either case. Operation in both cases confirmed the existence of lesions at the site of abnormality of the nerve after injection of the oil.

N. SAVITSKY, New York.

Treatment, Neurosurgery

COMPOUND, COMMINUTED SKULL FRACTURES PRODUCED BY MISSILES. E. H. CAMPBELL JR., *Ann. Surg.* **122**:375 (Sept.) 1945.

Summarizing his observations on 100 cases of compound, comminuted fractures of the skull, Campbell says that inner table fractures were sometimes overlooked and occasionally led to serious complications. Tripod incisions often gave trouble; it is recommended that they be avoided when possible. Convulsions were uncommon in the first few weeks; their occurrence was sometimes an early manifestation of abscess formation. Subdural hematoma was present in but 2 cases. Superficial wound infections of varying degrees developed in 19 cases, while in 22 the infections were deep seated. These were manifested by abscess, meningitis or cerebral fungus. There were 5 deaths, all of which occurred in the latter group. Incomplete débridement was the largest single factor contributing to wound infection. In those cases in which all bone fragments had been removed infection was uncommon and seldom deep, whereas if débridement had been incomplete or not performed infection was common and usually deep. Bacteria cultured from these wounds were principally skin inhabitants of low virulence. Treatment consisted in evacuation of pus and removal of associated bone fragments and/or metallic foreign bodies as well as of adjacent necrotic tissue and old blood. Abscess capsules were disturbed as little as possible. Sulfonamide therapy was employed as an adjuvant. Failures resulted only in those 5 cases in which, for one reason or another, this procedure was not carried out. Experience, judgment and skill, as well as the proper neurosurgical armamentarium, are prerequisite to good primary débridement.

J. A. M. A.

REHABILITATION OF PATIENTS TOTALLY PARALYZED BELOW THE WAIST, WITH SPECIAL REFERENCE TO MAKING THEM AMBULATORY AND CAPABLE OF EARNING THEIR LIVING: I. ANTERIOR RHIZOTOMY FOR SPASTIC PARAPLEGIA. D. MUNRO, *New England J. Med.* **233**:453 (Oct. 18) 1945.

Munro asserts that a patient with an injury to the spinal cord or cauda equina who is intelligent and cooperative and has the use of the shoulder, arm and hand muscles can be made ambulatory, can have such control of the bladder and bowels as to sleep through the night without either getting up or wetting himself, can carry out ordinary activities throughout the day without soiling himself with feces or having to evacuate his bladder oftener than once every three hours, can lead a normal social life and can earn a living. This paper is the first of a series that describes certain therapeutic procedures that have made the attainment of these end results possible. The author has performed a bilateral dorsolumbar anterior rhizotomy on 10 patients. This bilateral intraspinal division of the anterior roots of the eleventh thoracic through the first sacral spinal nerve is recommended as a means of changing a spastic to a flaccid paraplegia in patients with an anatomic transection of the spinal cord at any point between the second thoracic and the second sacral segment preliminary to making the patients ambulant and to providing them with complete twenty-four hour control of micturition, so that they may again become active members of their community and be self supporting.

Because this operation is a permanently destructive one, the indications for performing it should never be considered lightly. For the present, at least, it should be strictly limited to patients in whom the spinal cord is anatomically transected and in whom all neural connections between the cut surfaces of the cord have been destroyed.

J. A. M. A.

PENTOTHAL SODIUM ANESTHESIA IN NEUROLOGIC SURGERY. EDWARD W. SHANNON and W. JAMES GARDNER, *New England J. Med.* **234:15** (Jan. 5) 1946.

The study was made on 101 unselected neurosurgical patients who were cared for at the Cleveland Clinic. Pentothal sodium anesthesia was induced in these patients and "in several hundred major neurosurgical procedures." No death could be attributed to the anesthetic.

The technic employed consisted of administration of an enema and 0.1 Gm. of seconal sodium the night before the operation. The meal before the operation was omitted, and 0.1 Gm. of seconal sodium was given two hours before the operation. Forty-five minutes prior to operation adults received 0.65 mg. of atropine sulfate and children a proportionately smaller dose. If the patient was unusually apprehensive, morphine was given with the atropine.

Pentothal sodium was administered in a 2.5 per cent solution via a side arm, which was connected to an apparatus for the intravenous administration of 5 per cent dextrose in isotonic solution of sodium chloride.

In the experience of these authors, pentothal sodium as an anesthetic is "superior to all others for craniotomy." The induction of anesthesia is brief, and the patient is under an anesthetic for a shorter time. The authors state that there is no increased intracranial pressure; hence, bleeding is reduced. Postoperative vomiting and retching are an unusual occurrence following pentothal sodium.

This anesthetic agent was successfully employed in all types of craniotomy and operations on the spinal cord. The authors conclude that induction of anesthesia with intravenous administration of pentothal sodium has been found to be extremely satisfactory and safe for neurologic surgery. GUTTMAN, Philadelphia.

TROPICAL HEADACHE: PRELIMINARY REPORT ON DIAGNOSIS AND TREATMENT. W. W. WOODS and J. W. STUTZMAN, *U. S. Nav. M. Bull.* **46:501** (April) 1946.

Woods and Stutzman examined 20 young men suffering from severe, incapacitating headache for which no specific cause could be found. Five patients had severe unilateral frontotemporal headaches; the remaining 15 patients had bilateral frontal headaches. The unilateral type is to be considered as caused by abnormal extracranial vasodilatation. The pain is conducted by afferent fibers coursing along the vessels and may often be relieved by selective arterial resection. The unilateral pain did not respond to therapy consisting of increased intake of salt, calcium and fluids or of injections of neostigmine methylsulfate. It was made worse by heat and exertion and by compression of the jugular vein produced by infection of a blood pressure cuff about the neck to 35 mm. of mercury for three minutes. The second type, represented by the 15 cases of bilateral frontal headache, is to be considered as arising from intracranial vascular structures. In all these cases the headache was made worse by heat and exertion but was often improved by compression of the jugular vein. Occlusion of the carotid artery seemed to relieve the headache on that side only and often made the pain worse on the opposite side. Occlusion of extracranial arteries had no effect. Since the headache was accompanied with decreased intracranial pressure in the upright position, was made worse by lowering the level further and was abolished by raising the pressure, it could be assumed that traction on the intracranial vessels was a factor. This type of headache was definitely relieved by increased intake of salt, calcium and fluids and by injections of neostigmine methylsulfate.

J. A. M. A.

TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS WITH SULFONAMIDES IN CONJUNCTION WITH HEMOPHILUS INFLUENZAE, TYPE B, RABBIT ANTISERUM. E. A. NORTH, H. WILSON and G. ANDERSON, M. J. Australia 1:215 (Feb. 16) 1946.

North and his associates discuss the treatment of children with Hemophilus influenzae meningitis at the Children's Hospital, Melbourne, and the Royal Alexandria Hospital for Children, Sydney. Of 157 children of all ages who did not receive specific treatment, 2 (1.2 per cent) recovered; of 150, who were treated with sulfonamide compounds, 32 (22 per cent) recovered; of 81 who were treated with sulfonamide drugs in conjunction with type B Hemophilus influenzae rabbit antiserum, 46 (56.8 per cent) recovered. Recovery under treatment was more frequent with each year of age. The poorer prognosis for very young children was probably due to delay in the beginning of specific treatment resulting from late diagnosis, in consequence of the difficulty of recognizing meningitis early in such children without resorting to lumbar puncture. It was possibly due also to the absence of natural antibodies in the blood of young children and to their relatively poor immunity to infection. One of the sulfonamide drugs should be given. A bacteriologic diagnosis should be urgently sought, and specific antibody contained in rabbit serum should be injected as soon as the diagnosis is reached.

J. A. M. A.

TREATMENT OF CEREBRAL ABSCESS WITH SULFONAMIDE COMPOUNDS. J. PIQUET, Presse méd. 54:87 (Feb. 9) 1946.

Piquet reports the results of sulfonamide therapy of 15 patients operated on for cerebral abscess of otitic origin. Nine had a cerebral abscess and 6 a cerebellar abscess. Six patients with cerebral abscess and 2 with cerebellar abscess recovered. Treatment consisted in surgical removal of the initial focus; drainage of the abscess, with an iodoform drain allowed to remain in the cavity, and occasionally of decompression. A dose of 8 to 10 Gm. of the sulfonamide compound was administered daily for one week, and treatment was continued with smaller doses, depending on the improvement. Two patients had recurrence of the abscess. Sulfonamide therapy apparently improves the prognosis of a cerebral abscess by checking the encephalitis in the adjacent area of the abscess, but control of the patient for the next three months is essential because of occasional recurrence. Increased cerebral pressure may be relieved by puncture of the dura in the area of the primary abscess. An iodoform drain should be placed in the cavity for two to three months and be changed every eight to ten days. Neither local nor general sulfonamide therapy was effective in cases of cerebellar abscess. It was demonstrated that the white substance of the brain fixed twice as much of the sulfonamide drug as the cerebellar tissue.

J. A. M. A.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Madelaine R. Brown, M.D., *Presiding*

Regular Meeting, Nov. 29, 1945

Tonic Effect of Insulin in Acute Alcoholism. DR. ETEM G. VASSAF, Boston, and DR. VOLTA R. HALL JR., Arlington, Mass.

A series of 43 patients admitted for treatment of uncomplicated acute alcoholism was presented. In addition to the usual regimen of a high calory, high vitamin diet; forcing of fluids; use of supplementary thiamine hydrochloride, an antacid and a bitters tonic; chloral and bromide sedation; physical therapy; occupational therapy; psychotherapy, and gradual withdrawal of alcohol over a maximum period of three days, these patients were given 10 units of insulin twenty minutes before meals two or three times a day without the administration of dextrose as such. A comparison of patients receiving insulin in this fashion with the controls showed results in favor of the insulin method: (1) The average period of withdrawal was reduced by one-half; (2) only one-third as many patients required or demanded whisky after admission; (3) there was increase in subjective ease and comfort during the period of withdrawal; (4) the amount of supplementary sedation required was markedly decreased, and (5) the average gain in weight, both during the first week of hospitalization and subsequently, was tripled. In spite of the insulin being covered only by the food of the subsequent meal, insulin reactions were rare and were readily controlled with oral administration of orange juice and cane sugar, although dextrose was always at hand for intravenous injection.

The clinical findings were discussed in the light of former laboratory studies on the relation of insulin and of dextrose to the oxidation and detoxification of alcohol and of clinical observations on the use of a combination of insulin and dextrose in treatment of simple acute alcoholism, as well as of the more severe toxic states, such as delirium tremens. It was suggested that the action of insulin may be due not only to its indirect effect in the detoxification of alcohol, via its furtherance of oxidation of dextrose, but also to a direct effect of the insulin itself, as certain previous studies have indicated.

It was pointed out that the addition of small doses of insulin alone to the regimen of treatment of acute alcoholism is of distinct clinical value and that the results compare favorably with those of the combined administration of insulin and dextrose. The treatment is recommended as a valuable addition to the therapy of acute alcoholism.

DISCUSSION

DR. W. H. FORBES, Brookline, Mass.: I was much interested in this paper, but I am handicapped in discussing it because most of the material is outside the realm of my experience. Such work as I have done along this line has not yet been published. It was started in cooperation with Mr. Norman Riung but was never completed, as he, who was the more active partner, was killed during the war. The studies about which we have just heard were concerned with chronic alcoholism. Those carried by Riung and me dealt only with acute alcoholism. Fasting subjects drank 2 ounces (60 cc.) of whisky (100 proof) mixed with water and then performed a series of psychologic tests. After establishing a curve showing the normal response to this dose, we gave the subjects either dextrose or insulin (or in some experiments we altered the oxygen tension), with striking results, which, however, differed materially from those just presented. Either dextrose or oxygen produced striking improvement in performance, whereas insulin or a

low oxygen tension caused great deterioration. These results are dependent, however, on making the observations within the first two hours after administration of the alcohol. After that period our results were quantitatively very different. The best period in which to show the effects of insulin or dextrose was one-half hour after the ingestion of the alcohol, at which time both its concentration in the blood and its effect on the performance of the subject were at their peak. The injection of 2 units of insulin at this time, a dose which would have a barely perceptible effect on the normal person, caused the subjects who had taken the alcohol almost to pass out. The test we used principally was the Johnson code test, and with the average subject the length of time taken to perform the test was increased by the dose of alcohol by about 25 per cent. For the subjects who had insulin without alcohol the increase was about 10 per cent, but the subjects who had both alcohol and insulin were unable even to write, let alone to do any coding or decoding.

The oxidation of the alcohol during the first hour did not seem to be greatly influenced by either dextrose or insulin. The improvement due to the giving of dextrose and the deterioration due to the injection of insulin were not attributable to the level of alcohol in the blood, as this was the same in the controls and in the two experimental conditions.

I am inclined to think that the picture after an alcoholic bout of considerable duration is quite different from the picture we were studying. This impression is based on observations at the Boston City Hospital in which my associates and I gave dextrose to subjects in the ward for alcoholic patients. Some of the patients who had taken alcohol very recently showed dramatic reduction in the level of intoxication, but the subjects who had been consuming large quantities of alcohol for some time showed negligible effects of the dextrose. We did no experiments with insulin at this hospital.

DR. JOSEPH THIMANN: I gave insulin to 16 acutely intoxicated patients, according to the method of Tillim. The ages of the patients varied from 27 to 61 years. The length of the last drinking spell ranged from three days to nine weeks. For the majority of patients it lasted about one week. The amount of whisky consumed during the last spell varied from 1 pint to 2 quarts ($\frac{1}{2}$ to 2 liters). One patient consumed a gallon (3.8 liters) of whisky in three days. Five of the patients were "repeaters," giving me an opportunity to compare the insulin treatment with the conventional method of paraldehyde therapy, supplemented if necessary with dextrose, insulin and vitamins. In 11 of the 16 cases both patient and staff felt that the insulin method was definitely superior. In 4 cases the effect was as good as that of paraldehyde. In 1 case it was our opinion that paraldehyde therapy would have been the method of choice. It might be preferred in the management of severe delirium. The majority of patients recovered from the acute intoxication with fewer side effects than with paraldehyde. For 1 patient, aged 33, it was his second admission. His drinking spells were periodic. His last bout had started one month before. He drank more than a quart (liter) of whisky a day. He had had no solid food for the week preceding admission. On admission he was moderately intoxicated, with unsteady gait. He was fairly cooperative. The pulse was regular with a rate of 100; the blood pressure was 150 systolic and 90 diastolic. Tendon reflexes were absent in the lower extremities and hypoactive in the upper extremities. He received 60 units of insulin intramuscularly at 6:20 p. m. An hour later, he was asleep and his pulse rate was 110; he perspired moderately, and respiration and color were good. Two hours later, when roused, he said he felt well but was hungry and thirsty. Thirty minutes later, two hours after the injection, he was perspiring profusely; the blood pressure was 170 systolic and 110 diastolic. He received orange juice with sucrose. At 1:15 a. m. he could not sleep. He was given 0.2 Gm. of phanodorn. After that he slept until morning. He felt fairly well and was transferred from the ward to a private room. There was no nervousness. It appears that the insulin treatment of this patient was more successful than the conventional method; during his

previous stay at the hospital he was less heavily intoxicated on admission but had to be given 22 cc. of paraldehyde on his first day, 18 cc. on his second day and was unable to leave the admitting ward before the third day, and did not feel well even then.

In addition to these advantages, it is, in my opinion, especially gratifying that insulin therapy enables one to avoid treating the effects of one depressant (alcohol) with another depressant (paraldehyde). The insulin method will also take away the ammunition from those patients who, resenting the sudden withdrawal of alcohol, say sneeringly that paraldehyde is nothing but alcohol mixed with formaldehyde so they might as well taper off with a few drinks. Insulin treatment would also probably obviate addiction to paraldehyde in those "old timers" who make futile attempts to taper off with the help of self-prescribed paraldehyde.

I should like to refer to an article by Lolli and Greenberg, of Yale University (Effect of Insulin on Rate or Disappearance of Alcohol from the Stomach, *Quart. J. Studies on Alcohol* 3:92 [June] 1942). The authors of this article stated the belief that they had demonstrated that insulin induces more rapid gastric emptying and thus may increase the concentration of alcohol in the blood. In view of the fact that this observation may not be irrelevant in cases in which the alcohol level of the blood is high, bordering on the production of alcoholic coma, I wonder what Dr. Vassaf and Dr. Hall would think of preceding the insulin treatment by an injection of emetine hydrochloride, thus emptying the alcoholic contents of the stomach outward instead of into the blood.

DR. JOHN A. ABBOTT: I believe that you value insulin highly for its sedative effect.

DR. ETEM G. VASSAF: Our purpose in presenting this paper was to show that the method is simple and does not require a high degree of teamwork on the part of nurses and attendants. Patients receiving larger doses of insulin should, of course, get more carbohydrate in order to prevent any secondary reaction. Our findings, however, show that satisfactory results can be obtained with relatively small regular doses of insulin, without the necessity for large supplementary amounts of dextrose. We did, of course, stress an adequate food intake to make up for the poor diet which these patients have usually been receiving. We also noticed that dehydration was frequently an important factor and gave liberal amounts of fruit juices and other fluids. We did not give insulin intravenously because of its rapid, but short, action, which increases the possibility of coma, while lessening the therapeutic effect.

We were particularly impressed with the reduction possible in supplementary sedation. Paraldehyde has been used consistently in high doses in many institutions but is sometimes found to cause respiratory difficulties or to accentuate respiratory complications. Sometimes it has even been used intravenously; this is not good policy. Therefore, the less paraldehyde or other sedative used, the better.

DR. VOLTA R. HALL, Arlington, Mass.: As Dr. Thimann points out, insulin has an effect on gastric motility. But I do not think that the favorable results of insulin in these cases can be explained on that basis, since the effect of insulin obtains even into the second or third week. The use of emetine to empty the stomach of its alcohol promptly is theoretically sound, as in any case of acute poisoning by the oral route. From the practical point of view, however, its use might be limited by many patients being unwilling to present themselves for treatment at all if faced with the certainty of violent nausea and vomiting immediately on admission.

One meets something of the same problem in regard to the question of abrupt withdrawal versus tapering off. Doubtless, the former is the method of choice; but, again, many patients object strenuously to it. That we were able to accomplish immediate withdrawal in almost half our patients, without putting any pressure on them, or causing any hard feelings, is, we feel, worth while.

With regard to Dr. Forbes's observations, alcohol taken over a considerable period impairs glucose metabolism, and there is evidence that a certain amount

of glucose is present which cannot be utilized. In the cases described by Dr. Forbes, as he points out, the setting was somewhat different, but the results must be included in one's total thinking on the subject.

Incidentally, we had vaguely hoped that we might see a lowering in the rate of readmission. However, we cannot say that insulin makes any difference in the patient's psyche or in his propensity for intake of alcohol.

Syndrome of Cerebral Concussion from Air Blast. COMMANDER ROBERT S. SCHWAB (MC), U.S.N.R.

In World War I the syndrome of shell shock was given considerable prominence in the medical literature. The symptoms of the condition identified with this diagnosis were supposed to have been produced by the effect of blast from nearby exploding shells on the human brain. It was thought that the force of the blast transmitted through the air and into the cranial cavity destroyed the cytoarchitecture of the cortex by a sort of molecular disruption and that this cerebral damage produced the clinical signs that were associated with the condition. These were extreme irritability, strong startle reaction, bizarre tremors and automatic movements, some loss of memory, headaches and a striking decrease in efficiency. The absence of neurologic signs with these symptoms and the lack of other data that would indicate structural damage to the brain caused many investigators at the time to doubt whether these effects were due to the physical energy of the blast. The production of identical symptoms by factors other than nearby explosions, such as the violent, disruptive death of a companion or some other horrible emotional experience, as well as the successful treatment of many of the victims with purely psychiatric procedures, finally reduced shell shock to the category of a severe hysteria-anxiety syndrome and the term "shell shock" fell into disrepute.

In the recent war, as a result of the intensive bombing and greater destructive power and size of the explosives used, the term "blast concussion" appeared in the medical literature in 1940. It was supposed, as in the first world war, that these gigantic bomb blasts would result in direct damage to the brain. Various articles have been published on this syndrome, and it is an accepted diagnostic term in both the Army and the Navy.

The present report deals with clinical observations on about 350 patients seen in the Pacific theater in 1944-1945 who were admitted to naval hospitals with a diagnosis of "concussion, atmospheric, cerebral."

The first large group of patients who were observed were in a naval hospital in the Hawaiian Islands, to which over 100 men given this diagnosis were admitted. The second group consisted of 105 patients from Iwo Jima, and the third group, of 150 patients received during the Okinawa campaign; both groups were seen at Guam. A smaller group, of about 25 men from the Bougainville campaign, were examined in a hospital in New Hebrides. I saw about a dozen patients given this diagnosis at the Chelsea Naval Hospital in 1943; these men had received their initial blast effect the previous year on Guadalcanal.

Since all these patients had been exposed to the near blast of either bomb or shell explosions, it might be well at this point to describe the general effect of an air blast in the open and to relate personal observations on it.

I had an opportunity for temporary duty on a heavy cruiser which was engaged in battle practice involving considerable use of 8 inch (20 cm.) guns. Since this was not an actual battle condition, it was possible to be stationed on the wing of the bridge, about 20 feet (6 meters) from the 8 inch gun, during broadside fire. Knowing the damage to the ear drums from such proximity to these discharges, I insured against such injury by careful application of cotton in the auditory canals. The primary objective was to note the effect of pure blast and to determine whether it would produce headache or other uncomfortable sequelae. There was no danger, of course, in such a position of being injured by any fragments. For the better part of a day and one evening I stood by these guns to observe the effect of the blasts. In spite of the cotton in the ears, the blasts were exceed-

ingly unpleasant to the ears. The force of the air wave would push one about and tear one's shirt. A pair of spectacles was blown off in one of these blasts. The incandescent yellow flash, when observed directly in the daytime, rendered the eye blind for thirty to forty seconds. When observed once during the night, with the pupil dilated, temporary blindness lasted about four and a half minutes. No headache or other somatic disturbance was noted. The intensity of the blast effect was calculated by an ordnance expert as being about the same as that of a 100 pound bomb or shell exploding at the same distance.

As a result of this observation, it seemed unreasonable that the effect of pure blast would injure the brain in the cases observed. The nature of the blast wave is such that in the open atmosphere the compression effect is rapidly dissipated, so that a few yards away from the exploding missile the crushing effect of the air pressure has diminished to a degree that it could not damage a structure like the cranium. However, if it were intense enough, the compressing effect could very well crush soft organs containing air or fluids. One would suppose therefore that if the brain were damaged by such an effect there must always be extensive damage to the lungs, viscera, blood vessels, eyeball and sinuses. The ear drums, which respond to such pressure readily, would always be ruptured under such conditions. Now this is not the case. In 90 per cent of the patients seen the ear drums were intact. In all but 3 of the patients observed there was no evidence of blast effect in the organs aforementioned. Furthermore, in the 3 exceptions noted the blast did not occur in the open but took place in a confining space, where the effect of pressure could not be dissipated and where, therefore, the blast might be expected to produce compression effects on the brain. Neurologic examinations of these 3 patients revealed definitely abnormal signs. On the other hand, for well over 300 patients bearing this diagnosis the results of neurologic examination were within normal limits—clinical evidence that there was no cerebral damage. In a small group, i. e., 15 men, the spinal fluid was under normal pressure and free from red blood cells and increase in protein. In a larger series, i. e., 75 men, not seen by me, but reported on verbally by Lieutenant Commander Fogel, of the U. S. S. *Bountiful*, the spinal fluid was normal in all.

About 40 per cent of these patients complained of a definite period of amnesia, lasting anywhere from thirty minutes to thirty hours. It is this amnesia which has led many clinicians to the conclusion that cerebral damage must be present. Analysis of the amnesia in this group of patients reveals the following characteristics: None showed any retrograde amnesia. Retrograde amnesia is usually found in cases of damage to the brain from injury to the skull. In fact, the amnesia usually reported in this series began after the subject had heard the explosion and felt himself pushed down by its effect. In all cases in which the amnesia was explored by means of narcosynthesis (pentothal) or hypnosis restoration of memory was possible. This is not considered characteristic of the amnesia associated with cerebral damage. In many cases the amnesic material revealed a serious panic state with complete loss of control: violent fear reactions and surrender to the flight impulse. Of course, in well trained fighting men such behavior produces an intense feeling of guilt and shame, so intense that unconscious burial by means of amnesia is the only way out. In a number of cases exploration of the amnesia revealed a period of recall which ended shortly after an injection of morphine or a. barbiturate. This medication, then, produced a "natural" sleep, which could not be further explored and which certainly could not be explained by any means as a result of damage to the brain but, rather, was only the normal effect of strong sedation. Illustrative cases will now be described.

CASE 1.—A pharmacist's mate aged 19 was brought into the hospital by air with a diagnosis of air blast concussion, which had occurred twelve hours before on Okinawa. He had been in the front lines administering to the wounded for six days. He was suffering from deprivation of sleep, inadequate food and water intake and extreme fatigue. He had been under heavy artillery and mortar fire most of the time. His past history was free from neurotic illness or breakdown. The last thing he remembered was a shell exploding near him, and he woke up

in the evacuation airplane four hours later. Neurologic examination revealed nothing pathologic. There were a strong startle reaction, extreme anxiety, tremor of both hands and tremulous speech. Under pentothal narcosis he relived his battle experience readily, a summary of which follows: A mortar blast nearby pushed him on top of a patient to whom he was trying to administer plasma and spoiled the procedure. He began to shake violently at the time. He dragged his patient into a foxhole but was unable to give him any more first aid. The patient, he believed, was dead by that time. A sense of failure overwhelmed him. At that time he heard a terrific explosion above the foxhole, and then the period of amnesia began. During the pentothal narcosis he remembered crawling out of the foxhole, screaming and crying, and trying to get up on his feet and run toward the aid station. He passed two other wounded, or possibly dead, Marines during this struggle. Another corpsman aided him, put him into a tank or tractor and took him to the dressing station. He recalled being given some sedation and being wrapped in a blanket and put into an ambulance. He remembered crying and sobbing during the entire ambulance trip to the airfield. The intense guilt of this man's breakdown, occurring at a time when he was thoroughly exhausted, would cover the mechanism of the amnesia. There was no evidence whatever of damage to his brain; recovery took place in three weeks, and he was returned to duty.

CASE 2.—A Marine sergeant, after twelve days in the front lines at Iwo Jima under conditions of extremely heavy fighting, was in a trench when a large bomb or torpedo exploded nearby. He remembered being covered with black dust and hearing the noise of the explosion. He had amnesia for sixteen hours after this. Under pentothal narcosis, he recalled readily that he stayed in the foxhole, afraid to move, with the dust in his nose and mouth. He was picked up by a stretcher group and taken back to the beach, which was also under fire. On the landing vessel, which was taking him to the ship, he opened his eyes to witness the futile efforts of two corpsmen to save a man dying of a horrible wound of the throat, in spite of a physician's attempt to get in a tracheotomy tube. The retelling of this part of the episode brought out tremendous agitation, anxiety and hyperventilation. The patient improved greatly after the clearing of his amnesia with rest and sedation and probably was able to go back to noncombat duty after he left the hospital. There was certainly no evidence of an organic lesion of the brain in this case.

CASE 3.—A medical officer during an aerial bombardment was walking down the corridor of a landing ship tank, when a 200 pound bomb exploded in the adjoining passage, spraying an area with fragments 2 feet (60 cm.) in front of him. He was knocked down and was unconscious for a few minutes. He had no recollection of the blast or of the fragments hitting the wall in front of him. The last thing he remembered was leaving his cabin to go to his battle station. He showed bilaterally ruptured ear drums; loss of hearing, which was partially permanent; bleeding from the nose; moderate bleeding from the lungs; some bleeding from the intestinal tract; bilateral retinal hemorrhages, which cleared up, and definite weakness of the left leg, with a Babinski sign. He did not have the startle reaction, tremor and anxiety or other symptoms described in the preceding cases. There was an undisclosed number of red blood cells in the spinal fluid. All these signs disappeared except the loss of hearing, and he was able to return to duty three months later. This is 1 of the 3 cases in which a true air blast concussion was encountered and occurred in a confined space, where air pressure could be built up.

CASE 4.—A soldier, running across an open space between two hills in the front line, was thrown by a blast from a small mortar shell against a tree, striking his helmet so violently as to produce a large dent in it on the left side. He was dizzy for a minute and had a sharp tingling in his right foot. He did not lose consciousness. When admitted to the hospital, he had a large hematoma of the scalp; weakness of the right leg, which disappeared in two hours or so, and persistent left-sided headaches, which kept him on the sick list for some time

and eventually caused his evacuation to the United States. This man undoubtedly had a cerebral injury which was produced by his crashing into the tree, and not a blast concussion at all.

In conclusion, it is felt that in the vast majority of the so-called cases of air blast concussion—over 90 per cent—the condition is an extreme hysteroanxiety state produced in men who have been exhausted or otherwise conditioned to this form of trauma. There is no evidence in my observations of damage to the brain or the nervous system. A diagnosis of air blast concussion in these cases places the men in a surgical category that is not justified by the facts and deprives them of important prompt psychotherapy. It is regretted that no facilities for electroencephalographic recordings were available in this study.

DISCUSSION

DR. WILLIAM H. SWEET: I am much interested in Commander Schwab's account, for during a period of three and a half years of living in a British city (during the entire time that the United States was in the war), in which I was doing the neurosurgical work for a population of 1,000,000, no patients with blast concussion were admitted to the hospital. Incidentally, the British had a rather good system of utilizing personnel, in that internists and neurologists tended to put borderline cases into the hands of physicians because the surgeons were too busy. One group of cases which was taken over by the neurologists was that of the closed head injuries. These cases went to neurologists or psychiatrists instead of to neurosurgeons. Neurologists and neurosurgeons were on the same floor in the hospital with which I was affiliated, and they worked in close association. There were no cases of blast concussion at all. The series included civilian cases and several hundred military cases from Europe and North Africa. Of course, in civilians there is not the urge to get away from the scene that there is in fighting personnel on the battlefield. Perhaps this is one reason that the civilians do not tend to behave in the way described by Commander Schwab. In general, civilians who were scared or ran about were treated unsympathetically, and they were no problem in the ward. The 1 patient during the war whom I saw acting thus was denounced by the other patients. There was no disciplinary problem for the staff.

To take up a more positive aspect of air blast concussion, and to cite a few extraordinary cases, I may first refer to the statement that such a concussion cannot occur in an open space, outdoors. The most striking episode I know of was reported by Surgeon Rear Admiral Cecil P. G. Wakeley. It concerned a yeoman of signals, who was standing on the bridge of a boat when a bomb hit the boat well forward in the bows and killed a number of men. No one on the bridge felt anything except this yeoman, who had pain in his foot. He reported it to his officer, who told him to continue his work. The yeoman did so but, glancing down at his shoe, noticed blood coming out over the top of it. When the shoe was removed, the anterior third of his foot came away with the shoe; it had been sheared off without visible damage to the shoe. He was standing on some grid work, so that the air blast may have sheared his foot off.

There is an amusing case in the literature in which one can rule out psychoneurosis. The subject was a pheasant. Stewart, Russell and Cone, of the Royal Canadian Army Medical Corps, several hours after bombs had struck outdoors, saw a pheasant standing several feet from a bomb crater, with its eye closed. They could walk over, pick up the pheasant, put it down and push it, and it would take a few steps. It tended to keep whatever position it was put into. It reacted in a waxy, hypertonic fashion. It was not observed again for a long time because the game warden took it. However, when it was killed, a number of hemorrhages were observed in the frontal region of the brain, but there was no damage to the scalp or the skull.

At the Canadian Neurological Hospital they had several cases of a condition which they considered true air blast concussion. The symptoms were apathy,

depression and indifference to surroundings. In some cases the spinal fluid was xanthochromic.

Effects of blast can be exceedingly bizarre in the absence of any damage. There is a well authenticated case, described by Denis Williams, of a man who was sitting on a several thousand pound bomb, doing something to it, when the bomb blew up. No one expected to find even a fragment of the man. However, after the smoke cleared away, the man was found wandering around rather dazed. He was sent back to England from Malta, but no evidence of injury from this episode could be found, and the man had no complaints.

DR. HENRY R. VIETS: I congratulate Dr. Schwab on this excellent paper, and I concur fully with his findings. One may compare, as he has done, the observations in this war with those in the last. In 1918 the diagnosis of "shell shock" was widely used and covered many types of reactions. Ninety-five per cent of them fell into the class of psychogenic mechanisms. The other 5 per cent were due to air blast concussions in a confined space, such as a dugout. In some of this small group of cases petechial hemorrhages were present in the brain. There were also cases of parkinsonism resulting from concussion. Only cases of this type of "shell shock" can be compared with Dr. Schwab's underwater cases. Certainly, in most of the cases in both wars the disturbances were psychogenic. In the first world war, however, there was much more gross hysteria than in the second.

Dr. Schwab stated that amnesia was relatively rare in World War I. There were many cases of prolonged amnesia, with fugues. Men wandered about France, lost for months or weeks, without any recollection of who they were or what unit they belonged to.

It is disturbing to think that, with all the work on this subject in the first world war, one should meet a situation in the second war in which a diagnosis of air blast concussion was often made and patients treated as surgical emergencies.

DR. HERBERT I. HARRIS, Portsmouth, R. I.: I saw a number of cases at Okinawa similar to those Dr. Schwab has described so well. I think it is well not to rule out the organic possibilities entirely in considering this syndrome. Conceivably, an air blast of sufficient speed striking the skull and body from one direction could produce sufficient motion of the skull to produce contrecoup. In the great majority of cases, however, the syndrome does appear to have its origin in the emotional sphere.

DR. PAUL I. YAKOVLEV, Waltham, Mass.: From Dr. Schwab's interesting paper it appears to me that the effects of blast are due chiefly to the violent sound effect. The sudden and intense acoustic stimuli have a peculiarly jarring and widespread effect on the entire organism, certainly much greater than the effect of a sudden flash of even blinding light. In this respect the anxiety-producing effects of sound have their nearest equal in the "shocking" effects of a suffocating, pungent smell. It is of interest that the central synaptic surface of the acoustic system, like that of the olfactory, and in contrast to that of the visual system, is peculiarly widespread. It consists of a great number of overlapping neurons between the receptor organ and the thalamus. The acoustic system is also one of the most important pace makers of the synaptic processes in the entire central nervous system. This is shown by the fact that some persons may be thrown into a violent epileptic fit by a sudden loud sound. The hyperacusis in congenitally decerebrate persons and in experimental animal preparations is also well known. It would seem reasonable, therefore, to assume that the intense sound of blasts, especially under conditions of great emotional tension, may cause lasting changes in the synaptic surface of the central nervous system and that the disturbances in the emotional-affective sphere, the vertigo, headaches and other symptoms, are due to these central effects, with or without an injury to the peripheral acoustico-vestibular apparatus.

DR. G. COLKET CANER: I had the opportunity of seeing a number of these patients in a relocation center in Washington last winter. They were O. S. S.

men who had been dropped behind enemy lines and who worked with the resistance forces. Hardly any of them were subjected to severe shell fire. Practically all of them had the same syndrome. They were tense and restless, could not sit still long, were sleepless and had battle dreams and startle reactions. Many of them did not complain of symptoms in the field. They complained only after they had been out a week or more. While they were active and were using a great deal of energy, they were all right. When they got back to a quiet place, they became upset. This observation made me wonder whether the stress they had been under had overactivated the adrenal mechanism. The patients I saw quieted down after a number of weeks, but it took them quite a while to get straightened out. I wonder how much good it would have done them if they had been forced to recall their experiences under sodium amytal narcosis. If it was stress that made them sick, I should think that the stress of recalling their experience would have made them worse. It seems to me that it is the suggestions given while the patient is under sodium amytal narcosis that help, not the recall of traumatizing experiences. I should like to ask Dr. Schwab what he thinks about this.

DR. IVES HENDRICK: The subject is especially of historical interest, though it is a regrettable commentary on professional inertia that the history of shell shock revealed as a psychologic disturbance primarily motivated by anxiety should have to be repeated in the present war. Not until after the war is ended is there full recognition of the proper medical attitude toward these casualties.

Dr. Lawrence Kubie told me a most interesting detail of a careful investigation of these cases by abreaction methods; it was shown that the flash and light of the exploding shell was vividly recalled, but the sound of the explosion rarely, if ever. This observation may be unsubstantiated or may have been an artefact, but it suggests the possibility that this interval between perception of light and perception of sound represents the time during which amnesia sets in and, further, the possibility that any mental event so rapid as this may have its physiologic component.

Dr. Viets's comment on the differences in the syndrome in the two wars brings up an interesting aspect of psychologic and sociologic relations. It is undoubtedly true that although the basic phenomena of psychoanalysis are the same in different cultures, or in different periods of a culture, they give rise to different symptom formations. The most striking example of this is the rarity today of the major hysterias described by Charcot; so, in civilian practice one rarely sees major hysteria today, and the combat conditions of this war did not produce the combat neuroses of the last.

DR. JACOB E. FINESINGER: The fact that these patients with "concussion" show hyperactive reflexes and vasomotor instability, as do patients with combat fatigue, makes one wonder whether these patients have neurologic damage. I wonder whether one may not be dealing with a reaction which is in some instances irreversible. I am not sure whether available methods of examination are accurate enough to differentiate between no damage and slight damage to the brain. This differentiation is easier with patients who show evidence of distinct damage to the brain. In the last war some psychiatrists expressed the belief that a wound protected the patient from psychoneurosis. I should be interested in knowing whether a past history of psychoneurosis could be obtained from these patients with "blast concussion."

COMDR. ROBERT S. SCHWAB (MC), U. S. N. R.: The first point to be discussed is that brought out by Dr. Sweet concerning fractures of the ankle. He spoke of men who were standing on the deck of a ship and sustained such injuries when a bomb exploded nearby in the water. The Navy Department investigated a large number of these cases of fracture and found that the force of the explosion communicated to the ship through the water compressed the sides of the ship sufficiently to cause a sudden buckling effect on the deck, which was enough to fracture the foot of a man standing upright but would not fracture his bone if he were in a crouching position. This has nothing to do with air blast concussion, as the effect

in the case of fracture is transmitted through the water and the metal of the ship directly to the subject's foot. With respect to Dr. Sweet's comment on the pheasant and its neuropathologic changes, I can only state that I have read the article, and since it contained no accurate information about how the pheasant was injured I do not believe it proves anything. The bird might have fallen on its head. In answer to Dr. Viets, I stated that in these cases of so-called blast hysteria amnesia was present to a certain degree in 90 per cent, whereas the incidence was not so high as in the cases of shell shock reported in the literature. Dr. Harris' reference to the contrecoup effect is covered in Dr. Denny-Brown's review of the subject; it was felt that movements of the head with velocities great enough to produce this effect were not found in cases of air blast in either human subjects or experimental animals.

Dr. Yakovlev stressed the danger to the hearing apparatus. The journals of otolaryngology are full of reports of such damage, consisting of deafness, ruptured ear drum membranes and tinnitus. In most of the cases reported there were no neurologic or psychiatric symptoms. In the cases that I have described there were no such symptoms.

Dr. Caner's point is an interesting one. Pentothal has been helpful in cases in which there is not amnesia but repressed material of another sort.

Dr. Hendricks' comments were most interesting to me. In my interviews, a great many of the patients recalled the sound of the shell after the pentothal narcosis. However, they remembered much more vividly a flash of light, and the sound memory certainly was not the acute part of it.

I agree with what Dr. Finesinger says about a physiologic mechanism. I hope one will soon know whether or not abnormal emotional reactions are identical with abnormal physiologic states. A large number of these men, about 60 per cent, who suffered from this symptom had had neurotic episodes in their past lives. No doubt, if they had been interviewed in more detail as were those at the Massachusetts General Hospital by Dr. Finesinger a higher percentage of neurotic histories might have been obtained. It is important to emphasize that large numbers of troops went through the same amount of gunfire and did not break down, but continued to fight. I remember a soldier from the south who had the diagnosis of blast concussion on his card and who had amnesia. Under pentothal narcosis, he said that when the first shell went off and covered him with dirt he was in a place which was too dangerous for him to stay in. Another shell went off, and he lost consciousness. A third shell woke him up, and he crawled back to the aid station, where he fainted. It is difficult to see how the same physical trauma could produce amnesia on one occasion and an awakening on another unless it was through a psychologic mechanism. In many of these cases the patient had never been exposed to shell fire but the symptoms were produced from terrific emotional trauma alone.

In summary, I should like to emphasize again that it is possible to have damage to the brain from air blast, and, although there are undoubtedly cases of true concussion that have occurred, usually in confined spaces, over 90 per cent of cases are of the same pattern of the acute hysterical-anxiety symptoms one sees in other forms of sudden and acute emotional breakdown and the condition should be treated as a neurosis rather than as an injury to the brain. Some cases, to be sure, are of mixed type, with physical trauma, either head injury or damage elsewhere, associated with the neurosis. I have excluded these cases from my series whenever possible because of the complication of physical injury. I saw many cases of acute disorders on the beach in the Leyte campaign. They were identical with these cases of "blast concussion," but the condition was called battle fatigue. Whatever the diagnosis, the most efficient way of treating a patient with a war neurosis is to keep him in the combat area and treat him immediately. If he has a surgical condition, such as concussion, he must be evacuated to the rear; treatment, therefore, is postponed, and his chances of recovery are reduced.

Kenneth J. Tillotson, M.D., *Presiding**Regular Meeting, Feb. 21, 1946*

Mental and Performance Testing of Neurologic Patients. DR. EDWIN M. COLE, MISS MIRIAM P. BAGGETT and MISS MARJORIE R. MACMULLEN.

The work to be reported here is being carried on at the Massachusetts General Hospital, in an attempt to establish a testing program for use with neurologic patients and to obtain a battery of tests that will be useful in detecting impairment and will furnish a quantitative evaluation of impairment and a permanent record.

Many theories have been presented with respect to the type of loss or impairment characteristically present in organic disease of the brain. In general, loss seems to be greatest in memory and in functions or tasks which require spontaneous application of new concepts. Impairment being loss from a previous level of functioning, the task of measurement is made difficult by the need of a means of evaluating previous levels and capacities.

The present study is based on results obtained from 129 of 325 patients tested. Subjects were selected as a random sample from the neurologic wards of the Massachusetts General Hospital, and those included in this study were all between the ages of 15 and 59, inclusive; all were given both the complete Wechsler-Bellevue and the complete Hunt-Minnesota test, with a Wechsler-Bellevue score of 80 or above; and for all a relatively clearcut diagnosis on discharge was available from the clinical record. The cases were classified as follows:

I. Primary pathologic processes of the brain, i. e., changes involving the substance of the brain itself, such as toxic and degenerative conditions, infarctions, tumors and abscesses.

A. Cerebral disease: 24 cases	
Toxic delirium	2
Head injuries (post-traumatic cerebral syndrome and confusion of the brain).....	8
Extrapyramidal disease (Wilson's disease, encephalitis and birth injury).....	4
Encephalopathy or increased intracranial pressure of unknown cause	2
Cerebral degeneration (?), Alzheimer's disease.....	4
Cerebral infarction	3
Porencephalic cyst	1
	<hr/>
	24
B. Tumor and abscesses of the brain: 32 cases	
Unlocalized or suspected cerebral tumor.....	15
Specifically localized tumors and abscesses.....	17
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	32
II. Intracranial disease exclusive of cerebral tumor: 32 cases	
Epilepsy	16
Diseases primarily of the meninges.....	6
Extracerebral, but intracranial, tumors, meningiomas and osteomas	10
	<hr/>
	32
III. Control group: 41 cases	
Neurologic conditions without cerebral involvement..	33
Psychoneuroses	5
Hypertension	3
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	41

A careful history was obtained from all patients with respect to native tongue, educational level and language dominance. Tests used routinely included the Weschsler-Bellevue test for mental ability; the Hunt-Minnesota test for visual and auditory learning; Stanford achievement tests for reading, spelling and arithmetic; motor performance tests (including habitual skills, judging weights and test 5 of the Detroit tests of learning aptitude), and language tests.

Results.—Statistical analysis has shown that the groups tested were well matched as to age, the mean being 35 years; educational level (grade 9); intelligence quotient, and vocabulary level. Therefore, significant differences are apparently due

to a pathologic condition rather than to differences in age, education or intelligence quotient.

A significant difference between groups was found in the Hunt-Minnesota test as follows:

Group	Percentage with Pathologic Scores in Hunt Test
Cerebral disease	71
Cerebral tumor	61
Intracranial disease	57
Control	39

There was also for this test a statistically computed significant difference between mean scores for the group with cerebral disease and the control group, for the group with cerebral tumor and the control group and for the group with intracranial disease and the control group, although the ratio for the scores of the last two groups was significant only at the 0.05 level. The test neither eliminated all controls nor detected all cases with pathologic conditions, but the difference between group scores is sufficient to indicate that the test was effective significantly above the level of chance in discriminating between groups. Work with the Wechsler-Bellevue test showed that comprehension, digit symbol and picture completion tests were the tests most likely to indicate a pathologic condition.

Briefly stated, the results are as follows: For the group with cerebral disease, the scores for the comprehension and digit symbol tests differed significantly from the scores for the other subtests; for the group with cerebral tumor, the scores for the picture completion test, in addition to the scores for the comprehension and digit symbol tests, differed significantly; for the group with intracranial disease, the scores for the digit symbol and picture completion tests showed significant differences, but the score for the comprehension tests did not. The control group showed no consistent pattern of significant differences, and no subtest gave scores which differed significantly from the score for the comprehension, the digit symbol or the picture completion test. From such results it should be possible to establish differential scores that would provide quantitative indicators of the presence or absence of pathologic changes and the type of the pathologic process.

Of the standard achievement tests given, the spelling test proved most indicative. The control group demonstrated a normal curve for decline with age, while both the group with cerebral disease and the group with cerebral tumor measured reading comprehension and arithmetic computation at essentially equal levels, but spelling scores showed a conspicuous drop, especially in the group with cerebral disease. The group classified as having intracranial disease scored on spelling tests above the level of the other functions. This difference in pattern may, therefore, be considered in evaluating a total battery of tests.

In patients with organic disease of the brain, speed of performance was found to be diminished. In the use of tests requiring speed in performing habitual skills no significant differences were found between groups; that is, slow performance did not correlate significantly or consistently with pathologic change. In the Detroit Motor Speed Test in which precise pencil work is required, the patient used both the preferred and the nonpreferred hand, and the test was of interest in comparing the two sides rather than in determining speed, since, again, no group showed a consistent pattern. In judging weights, the most interesting finding was that ability to judge relative weights seemed to be correlated with the intelligence quotient.

A simple test, devised by Wells, for language disturbance was used in the form of comparing speed required for reading a list of words with speed required for naming colors. A ratio was obtained, and tentative norms were established. As with other tests which are without previous norms, further data must be accumulated, but the results suggest that the test is of use in detecting the presence of aphasia.

As a result of this work with a group of neurologic patients, the following conclusions can be drawn: 1. A clearcut quantitative record of the patient's abilities at the time of examination is obtained. 2. Variations in types of performance in terms of these tests are found with various pathologic processes, and these obser-

vations have been applied to the diagnosis for the specific patient. The results were particularly significant in cases of tumors of the brain substance and non-expanding lesions of the brain. Many extensive correlations need to be made, particularly with respect to other diagnostic procedures, such as examinations of the spinal fluid; ventriculographic, roentgenographic and electroencephalographic studies, and careful pathologic examinations, all of which, it is hoped, can be done in the future.

DISCUSSION

DR. F. L. WELLS: The amount of work represented in a special presentation such as this can best be appreciated by other workers in that specialty, and from this standpoint it has been a treat to listen to this paper, with its additional evidence that clinical psychometrics is getting beyond the "bug-hunting" stage of scientific observation, into the stage of systematic comparisons. To the sympathetic critic, the first suggestion of such a presentation is always, "Where does one go from here? What leads are opened up? How can one now do this better as a result of what has been done?"

As time goes on, the groups will of course be enlarged, which may somewhat modify the present indications: One thinks in this connection of the possibility of controls with other than neurologic diseases, after the manner of the work by Weisenburg, Roe and McBride in establishing adult norms for various intellectual functions. A research of this kind is not dependent on external norms and, having its own controls, is also independent of procedures developed elsewhere, and for other purposes. It seems quite likely that such procedures can be usefully refined on the basis of leads here given. There are some points at which item analysis may be useful—for example, in the Bellevue Information Test, the population of the United States, the discoverer of the North Pole or the definition of a thermometer; in the comprehension test, the reason that persons born deaf are unable to talk, or the likeness between a wagon and a bicycle. Moreover, unless evidence has appeared to the contrary, it might be well to inquire as to the differential performance with digits forward and backward, since the processes involved are very different.

It is perhaps not too early to consider some of the broader meanings of these observations. Until one has some notion of the reasons for these significant differences (and let it not be forgotten that statistical significance is not at all the same as pragmatic significance) one is on rather precarious interpretative ground, like the self medicator whose death was due to a misprint. How far is failure in the Bellevue comprehension test a reflection of poor judgment, or failure in the digit-symbol test a reflection of slowness in establishing new associations? Recently a close association has been posited between lowered digit span and anxiety, but other conditions may lower it quite as effectively. Anything will lower digit span that disturbs the capacity for controlled attention over short intervals; this is the essential thing to understand. One is justified in looking askance at test "profiles" of schizophrenia, organic conditions and the like. If schizophrenia, for example, really has any clearcut clinical meaning, and one understands that meaning, one will not need anyone to say whether or not some Bellevue response pattern is consistent with that meaning, and individual items of response will tell one far more about the presence of schizophrenic features than a pattern of subtest scores can possibly do. In attempting to understand what more general mental features these anomalies of test response have picked up, one will be in a situation to construct instruments of much greater effectiveness in spotting them.

A colleague of mine is, of course, in a different position, but I have often said that I would never let a student of mine get away with citing a global Bellevue intelligence quotient. Something was said about the correlation of weight perception with the intelligence quotient. One might consider whether it is not the higher mental processes which are involved in these discriminations generally, rather than any sensory factor. Indeed, the number of cases almost suggests another explanation, paralleled in an observation I recall with a small group of student

nurses, in which scores on the old Army Beta test had a correlation of about 70 with the alphabetical order of the names.

DR. EDWIN M. COLE: I wish to thank Dr. Wells for his discussion. He has given us much advice and many suggestions helpful in establishing our laboratory.

My intent has been to work out a test program which could be applied to a large number of neurologic patients. I felt it should be possible by means of these tests to pick up some cases of aphasia in the earlier stages, before they are otherwise readily observable. The tests must be applicable also to patients who have not had great experience or training in the use of English. Finally, since such a battery of tests is to be widely used and since the time allowance per patient is short, one is necessarily limited as to the amount of detail in such an examination.

Neurologic patients without apparent cerebral involvement were used as controls, since it seemed wise to use the same type of patients exposed to the same sort of conditions as control material.

Occlusion of the Basilar Artery: A Clinical and Pathologic Study. DR. CHARLES S. KUBIK and DR. RAYMOND D. ADAMS.

This paper will be published in full in *Brain*.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

Thomas J. Heldt, M.D., *President, in the Chair*

Regular Meeting, Detroit, Oct. 17, 1946

Protrusion of Cervical Intervertebral Disk. DR. ALBERT S. CRAWFORD and DR. HAWLEY S. SANFORD, Detroit.

Our present interest in the syndrome of cervical intervertebral disk stems from the report of Semmes and Murphey, who, in 1943, pointed out that disk material in the cervical area will often protrude laterally and not necessarily encroach on the spinal cord (Semmes, R. E., and Murphey, F.: *J. A. M. A.* **121**:1209, 1943). A monoradicular syndrome results. The present report adds 9 cases with operation to the literature. These 9 cases represent less than one third of the cases in which this diagnosis was made at the Henry Ford Hospital during the previous nine months.

There are several similarities between protruded disk in the cervical region and that in the lumbar area. In the cervical area the lower interspaces are usually involved, as they are in the lumbar region. These two areas are the points of maximum motion in the spinal column. Trauma plays an etiologic role in protrusion of cervical disk, although it may not be so violent or so well remembered as the trauma which precipitates a protrusion of the lumbar disk.

After the original injury, there follow "cricks" in the neck, which are reminiscent of the attacks of lumbago preceding the first attack of sciatica. In the cervical area, straining, coughing and sneezing will also aggravate the pain. Division of the scalenus anticus muscle, which may be in spasm, often gives temporary relief from the pain following protrusion of a cervical disk, similar to the results following Ober's operation for herniation of a lumbar disk. Doubtless, in the past, protrusion of a cervical disk has been diagnosed as the scalenus anticus syndrome, as well as brachial neuralgia due to arthritis of the cervical portion of the spine.

The characteristic monoradicular syndrome for herniations of the fifth and sixth cervical disks was described. The technic of the "foraminal compression test," as described by Spurling, was emphasized, with special attention to keeping the neck hyperextended as well as tilted. This test should be made with caution, and preferably only once on any one patient.

Contrary to some reports, myelography is quite satisfactory in demonstrating protrusion of cervical disk. It is of importance to use enough "pantopaque" (a

mixture of ethyl esters of isomeric iodophenylundecylic acid), preferably 6 cc., the needle being introduced in the fifth lumbar interspace. After the "pantopaque" has been injected, the head of the fluoroscopy table is lowered, the patient's neck hyperextended and the medium allowed to pool in the cervical part of the spinal canal. The defect is usually demonstrated satisfactorily. It has been found that the "pantopaque" is removed most rapidly with the cooperation of the patient and the examiner. The patient repeatedly performs the Valsalva maneuver, trying forcibly to expel air against his closed air passages. This supposedly causes engorgement of veins in the epidural space. At least it compresses the dural sac and causes the "pantopaque" to flow out through the needle. At the same time, gentle suction is made by syringe. With this method we have been able to remove practically all the "pantopaque" which can be seen fluoroscopically.

The symptoms of protrusion of cervical disk seem to be relieved more readily by nonoperative measures than is true of the symptoms following protrusion of lumbar disk. Perhaps this is due to the structures, namely, tendons and muscles, being smaller in the cervical area and more influenced by stretching procedures. Our present mode of therapy is daily diathermic applications to the cervical muscles, followed by four or five "pull-ups" of five minutes each in the Sayre halter traction. This treatment should be continued for at least two weeks. Traction of the neck at night seems to have little value.

In reviewing the surgical considerations, several anatomic factors are considered, particularly the narrowing of the foramina in the dorsoventral plane, the relative crowding of the cervical portion of the canal with nerve tissue and the close approximation of the nerve roots to the disk in the lower cervical region. Two types of pathologic changes are encountered: (1) hard (segment of annulus detached), with a clearcut history and findings, and (2) soft (nucleus pulposus), with a history of intermittent symptoms and insidious onset with respect to location; the central type is usually larger and more likely to give signs referable to the cord, while the lateral type is smaller and is likely to give few or no such signs but is characterized rather by local signs and disturbances referable to the nerve root.

The indications for surgical exploration are (1) recurring attacks with increasing severity of pain; (2) failure to respond to conservative management in two or three weeks; (3) progression of sensory and/or motor signs; (4) chronic state, with signs of localized pressure on a nerve root. Exposure is made by hemilaminectomy with the use of local or general anesthesia, and sufficient bone is removed to facilitate excision of the protruded segment and to give adequate decompression of the involved nerve root.

The results are satisfactory in the majority of cases. First, pain disappears; then the sensory and motor functions return to normal. The time required depends on the extent of the lesion and the duration of involvement at the time of operation.

Protamide Therapy for the Pain of Tabes Dorsalis. DR. RUSSELL T. COSTELLO, Detroit.

This article will be published in another journal.

NEW YORK NEUROLOGICAL SOCIETY

Joseph H. Globus, M.D., *President, in the Chair*

Regular Meeting, May 7, 1946

Dumb-Bell Tumors of the Spinal Cord: Report of Two Cases. DR. BERNARD C. MEYER (by invitation).

Two patients showing extramedullary tumors of the cervical portion of the cord with atypical features were presented from the neurologic service of the Mount

Sinai Hospital (New York). The first, a 20 year old student, first noticed numbness and dysesthesia of the right hand one year before hospitalization. Later stabbing pains began in the right arm. Later, numbness of the right side of the trunk developed, followed by a swollen feeling in the right foot. These symptoms were accompanied with difficulty in using the right arm and in walking. Examination revealed mild right hemiparesis, involving more especially the upper limb; signs on the right side referable to the pyramidal tract and impairment of deep sensibility on the same side. A level of hypalgesia and hypesthesia was noted at the fourth cervical and, again, at the third dorsal dermatome, especially on the left side, indicative of partial Brown-Séquard syndrome. Studies of the spinal fluid revealed no block; the protein content was 12.6 mg. per hundred cubic centimeters. Roentgenographic examination of the cervical portion of the spine disclosed destruction of the right lamina of the fifth vertebra with some involvement of the body of the vertebra. Laminectomy revealed a dumb-bell-shaped tumor arising from the fourth anterior root; the growth was both intradural and extradural. The extradural part, extending through the intervertebral foramen, was about twice the size of the intradural portion. Recovery followed the removal. The tumor proved to be a neurofibroma.

The second patient, a housewife aged 36, was admitted to the hospital one year after the onset of fatigue and paresthesias in the fingers of the right hand, which was followed by transient weakness of the legs. Weakness of the arm continued and was followed by numbness of the right side of the chest and later by weakness of the right leg. Examination revealed weakness of the right arm with some winging of the scapula. Signs referable to the pyramidal tract were noted in all four limbs, chiefly on the right side. Vibratory sense was absent in both legs and diminished in the right arm. Analgesia was present on the right side from the fourth cervical to the tenth thoracic dermatome, below which a zone of hypalgesia extended to the third lumbar dermatome. The right pupil was narrower than the left. There was no spinal fluid block, and the protein content was normal—46 mg. per hundred cubic centimeters. Postoperative roentgenologic studies of the cervical portion of the spine, originally considered normal, revealed destruction of the laminae of the second vertebra. The symptoms fluctuated during the early part of her hospitalization. Myelographic study was unsuccessful. Despite the uncertainty of the diagnosis, exploration was attempted. On two occasions, however, the patient went into shock, even before anesthesia had been started. On a third attempt, despite a systolic pressure of 60 mm., the operation was begun, exposing a large extradural tumor in the upper cervical region, which at the level of the second cervical vertebra was even extravertebral. The tumor extended intraspinally anterior to the dura. Severe hemorrhage necessitated closure, which was followed by quadriplegia. One week later the entire tumor was removed, which was followed by an excellent recovery. The tumor was a neurofibroma.

These cases are presented because, despite the generally accepted belief that extramedullary tumors of the cord are associated either with an increase in the protein content of the spinal fluid or with manometric block or with both, no abnormality of the spinal fluid was revealed in either. It is evident, therefore, that the absence of spinal fluid block or of elevation of the protein content does not exclude the possibility of extramedullary tumor of the cervical portion of the spinal cord.

DISCUSSION

DR. IRA COHEN: As Dr. Meyer pointed out, one not infrequently is put to it in the diagnosis of extramedullary tumors of the cord, particularly those of the high cervical region, which do not follow what one is pleased to call a typical pattern. The second case is a good example of this. The patient was under observation for three months; not only because of her peculiar behavior in the operating room prior to administration of the anesthetic, but also because of her possible improvement, we were loath to do an exploration; yet she had an extramedullary tumor, which was removed. The first case that Dr. Meyer presented

is of particular interest to the neurosurgeon, because a few days after operation spinal fluid accumulated in the tissues of the neck and there developed fever of unexplained origin, which occasionally occurs after suboccipital craniotomy. For several weeks the patient had a spiking fever, in spite of administration of various drugs (there was no infection, but he was treated as though there might have been). The collection of fluid disappeared suddenly, and the temperature dropped to normal and remained there.

As to dumb-bell tumors in general, there is nothing peculiar about them from the neurologic or the diagnostic standpoint except that they almost invariably give roentgenologic evidence of their presence. They may be extradural and intradural, or extradural and extravertebral or intradural and extravertebral. As a class they are not of particular interest from the diagnostic standpoint; neither are they of particular interest to the neurologist, but they are of interest to the neurosurgeon because of technical difficulties on the operating table, and they may well be of interest to the general surgeon.

I should like to show a roentgenogram of a patient who came with tremendous destruction of the cervical vertebrae, with a mass in her neck which was as large as a good-sized lemon. A biopsy had been done, but no attention had been paid to the rest of the neurologic signs. It is clear that dumb-bell tumors in the cervical region may well come under the care of a general surgeon, who should keep in mind that there is such a thing as an intraspinal extension.

This type of tumor may also be of interest to the thoracic surgeon. A patient may present such a tumor as this one, but with symptoms from the intraspinal part, and not from the part of the tumor in the posterior mediastinum. Such a tumor is the joint concern of the neurosurgeon and the thoracic surgeon. On the other hand, if there are no symptoms referable to the spinal cord, it can be tragic when the thoracic surgeon does not consider the possibility of a dumb-bell tumor, as was my experience when I was called to see a patient in another institution from whom a posterior mediastinal tumor had been removed. There had been some bleeding, and the surgeon had packed down to the bleeding point. When the patient awakened from the anesthesia, he was paraplegic. He had a spinal block, and I operated, thinking there had been displacement of the intraspinal part of the tumor; instead I pulled out the packing from the spinal canal which had been used to stop the hemorrhage. The thoracic surgeon must remember that a mass in the mediastinum may be connected with an intraspinal tumor. It may be that these dumb-bell tumors are not so infrequent as one is prone to think; among 110 extra-medullary tumors, I have encountered 8 well defined dumb-bell tumors; so the proportion is a bit greater than is generally thought.

DR. LEO M. DAVIDOFF: These tumors can be extraordinarily benign. I encountered a case fourteen years ago, that of a middle-aged pharmacist, not unlike the second case reported here. There was severe hemorrhage at operation. These tumors grow out laterally and acquire a rich blood supply from the vertebral artery, and that is what happened in this case. I removed the intraspinal portion easily, but when I attempted to excise the extraspinal portion I was forced to stop. The patient improved after removal of the intraspinal part, and he is still maintaining his improvement, fourteen years later. He has never had the extradural portion removed, has had no other therapy and has returned to his job and continued working ever since. Thus, if the extraspinal portion is too vascular, it may not be a tragedy to let the patient retain his tumor and save his life.

Ophthalmoplegia with Reversal of Bell's Phenomenon Occurring in a Diabetic Patient. DR. EDWIN A. WEINSTEIN.

Bell's phenomenon is the associated upward rolling of the eyeballs that occurs with vigorous closure of the eyelids. It is particularly evident on the side of a peripheral paralysis of the facial nerve. Forceful closure of the eyelids is also associated with constriction of the pupil, which may be observed by holding the lids apart.

S. G., a housewife aged 32, was admitted to the Mount Sinai Hospital on Feb. 28, 1946, because of vertigo, diplopia and drooping of the left upper eyelid. The patient had been known to be diabetic since the age of 10 and had been admitted to the hospital on nine occasions, once in coma and several times for acidosis. She had been treated twice for bleeding from the gastrointestinal tract. Epistaxis was a frequent complaint, and it was noticed that the patient bruised easily. In 1943 she had an illness similar to the present one, when, after an infection of the upper respiratory tract, she complained of vertigo and diplopia. Examination revealed paralysis of the left external rectus muscle. The patient recovered completely from this episode, and her neurologic condition was normal until three weeks before the present admission, when she again experienced vertigo and diplopia after an infection of the upper respiratory tract. Examination on her admission showed the following abnormalities:

1. Pronounced arteriosclerotic changes in the retinal vessels with areas of degeneration and hemorrhage.

2. Complete ptosis of the left upper eyelid.

3. Paralysis of internal rotation and of upward and downward movements of the left eye.

4. Miosis of the left pupil, with a diameter of 1.5 mm., whereas the right pupil measured 4 mm. Both pupils failed to react in accommodation, whereas their reaction to light was brisk. Convergence was intact in the right eye.

5. No movement of the paralyzed (left) eyeball during elicitation of Bell's phenomenon, while the right eyeball moved down instead of up. The pupils did not contract, and at times the right pupil was seen to dilate.

The spinal fluid was clear, with a total protein content of 58 mg. per hundred cubic centimeters. Application of the tourniquet with a pressure of 100 mm. to the upper portion of the arm produced numerous petechiae within three minutes.

In the first few days after the patient's admission the left pupil gradually grew larger, so that it was 1 mm. larger than the right pupil. Two weeks after her admission the left levator palpebrae muscle began to regain power, and one week later the reversed Bell's phenomenon in the right eye had disappeared. When the right eye was closed forcibly, the right globe rotated upward and the pupil contracted. A pseudo-Graefe phenomenon was seen in the left eye, with improvement in the power of the left internal rectus muscle. When the patient looked to the right, the parietic lid rose. This persisted after all other ocular movements had been restored.

This case is presented for two reasons. First, it affords an excellent example of the lesions in the brain stem which are being encountered in young diabetic persons with increasing frequency. Second, it is of interest in connection with the clinical physiology of ocular movements. Patients with severe diabetes show a premature vascular aging. Many young diabetic patients who would otherwise have died have been kept alive with better means of administering insulin and more efficient measures of combating infection. Vascular damage is observed early in these patients. At the age of 19 and 20 changes in the retinal arteries and hemorrhages may be observed in the fundus. Diabetes affects mainly the finer vessels, so that involvement of the smaller vessels of the brain stem is comparatively commoner in diabetic patients than is thrombosis of the larger arteries of the cerebrum. In the experience of my associates and myself, diabetes has replaced syphilis as the most common agent in vascular disease of the brain stem in young people. All are familiar with the frequency with which diabetes is the cause of thrombosis of the posterior inferior cerebellar artery. The pons and midbrain may also be affected, as this case illustrates.

Bell's phenomenon, as well as other acts involving integration of the various cranial nerves, may be reproduced experimentally by electrical stimulation in the region of the central tegmental fasciculus (Weinstein, E. A., and Bender, M. B.: Integrated Facial Patterns Elicited by Stimulation of the Brain Stem, *ARCH. NEUROL. & PSYCHIAT.* 50:34 [July] 1943). Stimulation of the oculomotor or the

facial nerve or nucleus did not produce the phenomenon, nor could it be elicited from those cortical areas which produce closure of the eyelids. Its reversal thus furnishes presumptive clinical evidence of an intramedullary lesion of the brain stem.

DISCUSSION

DR. MORRIS B. BENDER: This paper brings to my mind several phenomena. As Dr. Weinstein stated, the so-called Bell phenomenon is a part of the associated movements of the eye occurring in closure of the eyelids. With closure of the eyes there is upward movement of the globe (Bell's phenomenon) and contraction of the pupil. In studying these movements in the monkey under experimental conditions, Dr. Weinstein and I were able to reproduce them by stimulating the central tegmental fasciculus. We tried to abolish Bell's phenomenon by destroying this area in the brain stem, but we were not successful. All we found was that the eyeball did not move completely upward; there was a slight movement above the horizontal meridian.

Dr. Weinstein also mentioned the pseudo-Graefe phenomenon. This is synkinetic retraction of the superior lid whenever the subject attempts to look down. As a rule this is due to a lesion in the oculomotor nerve. However, Dr. Weinstein said he believed that in this case the lesion was intramedullary, and I agree with him. The pseudo-Graefe phenomenon may occur with intramedullary lesions. I think its occurrence may be explained by taking into consideration what Dr. Walter Cannon called the law of denervation. This law was first postulated by Claude Bernard. He stated that once an organ is denervated it becomes extremely sensitive. It reacts to various stimuli whether natural (neural), chemical or mechanical. This law of denervation applies to peripheral organs as well as to the structures within the central nervous system.

It is known that if one cuts the oculomotor nerve, after a varying period, the oculomotor muscles become very sensitive to the action of acetylcholine and that when there is recovery of function it is very hard to get contraction of an individual muscle. The same is true for lesions of the facial nerve supplying the facial musculature. After lesions of these nerves most of the recovered movements are synkinetic. The synkinesias in the case of the oculomotor muscles may be due not only to indiscriminate regeneration of the oculomotor nerve rootlets within the midbrain, but also to increased sensitivity of the ganglion cells in the oculomotor nucleus. The increased sensitivity of the ganglion cells in the oculomotor nucleus may be due to a partial denervation as a result of the intramedullary lesion.

Analogous to the denervation of the cells of the oculomotor nucleus is that of the ganglion cells within the anterior horn as a result of lesions in the corticospinal tract. This, according to Cannon, may explain the increase in the tendon reflexes associated with lesions of the corticospinal tracts. The law of denervation, as postulated by Claude Bernard, should be seriously considered and investigated further, as suggested by Cannon. I am sure many puzzles in neurology would be cleared by such a study.

Origin of Tumor of the Midbrain. DR. J. M. FRIEDMAN (by invitation) and DR. L. GREENSTEIN (by invitation).

This paper will be published in a future issue of the ARCHIVES.

DISCUSSION

DR. JOSEPH H. GLOBUS, New York: Most neurologists are familiar with the fact that true tumors of the midbrain are rare, and I have often wondered why this is so. But before one can explain the infrequency with which they occur, it is necessary to establish the source of the formation of tumors in this region. A search of the embryonic factors gives satisfactory information. Developmental defects in the region of the aqueduct of Sylvius and blastomatous changes result in tumors, which, in turn, cause atresia of the aqueduct of Sylvius. Familiar also is another, more frequent, malformation in the aqueductal region, the so-called

stenosis, or atresia, of the iter, for which, though its existence was known for many years, almost a century, no satisfactory explanation has been advanced. It was thought this atresia was due to an acquired inflammatory disease, but I think that now the explanation has been found. The developmental defect which causes blastomatous changes, resulting in tumor formation, is also responsible for the aqueductal atresia seen in the newborn.

Why should tumors of this type be rare? In all probability the atresia occurs so early in the development of the organism that a fatal termination interrupts the process of tumor formation. On the other hand, the subependymal matrix in this region is relatively poor in cellular material, and the embryonic changes in the course of development are few; therefore the occurrence of blastomatous formations in that region is rare.

DR. LEO M. DAVIDOFF, New York: I can only confirm the statement that the occurrence of primary tumors in this region is rare.

Encephalopathy (Kernicterus) of Erythroblastosis Fetalis: Serologic Diagnosis and Pathogenesis. DR. ALEXANDER S. WIENER (by invitation) and DR. MATTHEW BRODY (by invitation).

During the past forty years there have been many clinical and pathologic studies of kernicterus, most of them describing a severe or fatal neurologic syndrome as a complication of a neonatal jaundice in infants with normal parents. Until recently there was no adequate explanation of this peculiar combination of cerebral and hepatic disease. By ascribing the disorder exclusively to the cholemia one could not account for the fact that with the severe jaundice of congenital atresia of the bile ducts kernicterus does not occur. With the discovery of the Rh factor (Landsteiner, K., and Wiener, A. S.: *Proc. Soc. Exper. Biol. & Med.* **43**:223 [Jan.] 1940), which was shown to be responsible for almost all intragroup transfusion reactions (Wiener, A. S., and Peters, H. R.: *Ann. Int. Med.* **13**:2306, 1940), Levine and associates suggested that the Rh factor was the antigen at fault in erythroblastosis (*J. A. M. A.* **116**:825 [March 1] 1941).

If an Rh-negative woman marries an Rh-positive man and has an Rh-positive child, in the great majority of cases no sensitization occurs. In 1 or 2 cases out of 50, the mother becomes sensitized, either through childbirth or through a previous transfusion with Rh-positive blood. Each subsequent pregnancy may increase her sensitivity. The antibodies produced traverse the placenta and produce one or another manifestation of erythroblastosis in the infant, or a stillbirth. While the Rh factor is responsible for the disease in 90 per cent of cases, in 10 per cent the ordinary A and B blood group factors or the Hr factor produces the sensitivity. It becomes evident that the mere demonstration that the mother is Rh negative and the infant, whose neurologic disorder or mental deficiency is ascribed to the Rh factor, is Rh positive proves nothing, since sensitivity only infrequently follows in such instances, and since sensitivity can also occur as a result of factors other than Rh. In order to prove serologically that such sensitivity exists, it is necessary to demonstrate in the blood of the mother antibodies that react with factors in the infant's blood. Recent work indicates that there are two main types of antibodies. One is bivalent in the chemical sense and causes agglutination. The other is univalent and requires special technics for its demonstration. We have found that in practically all our cases in which kernicterus or neurologic sequelae occurred we could demonstrate the presence of bivalent antibodies (agglutinins) in the blood of the mother. This led to the hypothesis that the type of the antibody determined the nature of the disease. Our theory proposes that agglutinins formed in the mother's serum traverse the placenta chiefly during the muscular activity of birth and produce agglutination thrombi in the vessels of the infant where circulation is slowest. In the lung, such agglutination thrombi can produce pulmonary hemorrhage. In the bone marrow, these agglutination thrombi stimulate the formation of erythroblasts, even in the absence of anemia. In the liver, they result in increased jaundice. In the brain, the agglutination thrombi cause damage to and

destruction of tissue. The damaged and destroyed brain tissue then picks up the bile pigment. Thus, jaundice of the nuclear masses of the brain (kernicterus) is the result of an *in vivo* staining reaction and is in itself of little clinical importance. We feel that it is the widespread damage produced by the agglutination thrombi in the brain that is important. Postmortem examinations in 3 cases of kernicterus seem to confirm our theory.

For the sake of completeness, it may be said that the univalent antibodies—glutinins, or blocking serums—are smaller and traverse the placenta earlier in pregnancy, producing hemolytic anemia and hydrops fetalis without neurologic sequelae. If dehydration is present, then univalent antibodies may produce conglutination *in vivo*, with results akin to agglutination.

Examination in 3 cases of hepatolenticular degeneration failed to demonstrate any evidence of isoimmunization. Our theory, then, does not account for all instances of hepatic-cerebral disease.

This paper was published in full in the July 1946 issue of the *American Journal of Mental Deficiency*, pages 1 to 14.

DISCUSSION

DR. TRACY J. PUTNAM: I have learned a great deal from this admirable paper, the conclusions of which seem to me to be conservative. I am not competent to discuss the serologic aspects of the paper, but there is in my mind no doubt that the slides show obstruction of the venules and capillaries which is sufficient to account for the lesions, and it seems to me there is much to be said for the thesis that this obstruction of vessels leads to the necrosis, or partial necrosis, of the basal ganglia, and that this is a sufficient explanation of the yellow staining of the basal ganglia in these cases. I once had the opportunity of studying a case of carbon monoxide poisoning which offers interesting parallels, for in this case the patient was treated with injections of methylene blue, or was given methylene blue intravenously, a form of treatment which was popular at the time. It was not life saving in this instance. However, the patient survived long enough for the methylene blue to produce an exquisite intravital staining of the necrotic areas in the basal ganglia and elsewhere, but not of the living brain substance. It was quite clear that the necroses were not confined to the basal ganglia. The basal ganglia were clearly necrotic; the tissue was definitely softened, and the structure could barely be made out. However, it was quite clear that the structure had many resemblances to the venules and capillaries that we have just seen. That is, the venules were enormously dilated beyond their ordinary proportions, and the capillaries were widely distended as compared with the normal size. In that case, and I believe in practically all cases of late death in carbon monoxide poisoning, there were also focal necroses in the white matter. These have not been widely emphasized, but they are practically always present; there is an example in MacCallum's "Textbook of Pathology" showing this phenomenon of striking necrosis in the basal ganglia with striking small necroses distant from the basal ganglia in the white matter, obviously of the same nature, for in the center of these areas of necrosis there is a distended, obstructed vein much as in those seen on the screen. In this connection, I should like to ask the authors whether they found any small areas of necrosis or of yellow staining in the white matter. I should expect it to occur in the white matter with this widespread necrosis of the basal ganglia. I may say that the specimens of kernicterus I have seen, which have not been numerous, have not shown as definite and striking a necrosis as is apt to occur with carbon monoxide poisoning. Certainly, the late effect, such as is seen in the encephalogram, would suggest that serious tissue damage had occurred, and it is possible of course that in the brains of babies dying shortly after birth there are widespread areas of cellular destruction without disintegration, and that the cellular disintegration is a late stage of this process. I should appreciate a further discussion of this point. I should also like to ask the authors whether, in their opinion, the same mechanism is responsible for the atrophy of the basal ganglia in other clinical types of disease of the basal ganglia, such as bilateral

athetosis and dystonia. The pathologic process is in some instances extremely obscure and vaguely suggestive of some such process as this. It is certainly not well explained by any theories yet proposed.

I am sure that the authors are right in attributing this peculiar localization to the unusual blood supply of the basal ganglia, which is striking in specimens injected with india ink or in those stained with the benzidine method. It becomes clear that the capillary architecture in the basal ganglia differs from that in any of the vascular areas of the cortex. In the cortex there is a gradual and early transition from one size of the small arteries to the arteriole, and so to the capillaries, and through the capillaries to the venules, and then to small and then to large veins. In the basal ganglia, however, it is striking that the capillaries are of extremely small caliber, just barely sufficient to transmit a red cell, that they spring suddenly from rather large arteries and end in moderate-sized veins; that is, arterioles and venules are comparatively sparse in the basal ganglia as compared with the cortical areas, and they are both quite different in structure from the extremely sparse vessels of the white matter.

DR. PHILIP LEVINE (by invitation): Kernicterus is known only as a pathologic entity, but it now becomes important for the neurologist to see the erythroblastotic infants soon after birth for the detection of symptoms referable to pathologic changes in the brain. I share the view of the well known British pediatrician Dr. L. G. Parsons, cited in an editorial, published in the *British Medical Journal* (2:188, 1945) that if the diagnosis can be correctly made shortly after birth such an infant should not be treated but, rather, should be allowed to die.

The observations of Dr. Wiener and Dr. Brody have a certain amount of logic, but closer scrutiny of their views on kernicterus (Wiener, A. S., and Brody, M.: *Science* 103:570, 1946) and of Dr. Wiener's entire concept of blocking antibodies and agglutinins reveals glaring defects. In the first place, the sections from only 1 case are presented, and if the agglutinative thrombi in the blood vessels of the brain represent the end result of a specific antigen-antibody reaction, such lesions should be demonstrated in many other tissues, particularly in the kidney. To my knowledge, oliguria, anuria or renal lesion, other than evidence of extra-medullary hemopoiesis, has not been described.

Presumably, the authors are willing to gamble on observations in only 1 case. Were their views correct, kernicterus would be associated exclusively with erythroblastosis. However, this condition has been described by Dr. S. Farber, of the Children's Hospital in Boston, in patients who never had symptoms of this disease. In an oral communication, he tells me that a complete pathologic study of 55 cases of kernicterus failed to reveal the presence of agglutinative thrombi in the brain. Furthermore, Dr. Farber has observed kernicterus in premature and full term infants, irrespective of the presence of jaundice or erythroblastosis.

If agglutinative thrombi do represent the specific lesion in kernicterus, then one should expect a closer relationship of kernicterus to the presence of anti-Rh agglutinins in the mother's serum. In the first place, kernicterus is rare, while anti-Rh agglutinins can be demonstrated in somewhat better than 50 per cent of all Rh-negative mothers soon after delivery. A review of my own cases shows that the recovered erythroblastotic infants in the vast majority of cases in which the mother had powerful anti-Rh agglutinins remained normal and free from all symptoms. Furthermore, when the erythroblastotic infants did manifest symptoms of kernicterus, this development was not always correlated with the agglutinin titer. Finally, kernicterus was observed in instances in which the mother had no anti-Rh agglutinins but only blocking antibodies.

Aside from these considerations, Dr. Wiener's concept that anti-Rh agglutinins are of larger molecular size than blocking antibodies must be considered as purely hypothetical. One might expect to have heard from Dr. Wiener and Dr. Brody data on physical measurements of these contrasting antibodies, but, to my knowledge, all the evidence presented is indirect. Furthermore, passage through the placenta may depend on shape and electric charge of the molecule rather than on size.

The clearcut separation of forms of erythroblastosis on the basis of the presence of blocking antibodies or agglutinins cannot be confirmed by other workers in the field. I have seen infants with pure hemolytic symptoms in which the mother's serum showed the presence of strong anti-Rh agglutinins and no blocking antibodies. Dr. Wiener expresses the belief that in these cases only minute amounts of blocking antibodies could be held responsible for the hemolytic symptom, but the burden of proof of demonstrating the presence of weak blocking antibodies in a serum which shows a high titer of agglutinins and no zone phenomenon rests entirely on his shoulders.

Still more amazing is Dr. Wiener's use of the term "conglutination reaction" for the test with serum-suspended cells. In the first place, Dr. Wiener's concept of the elements in serum required to bring about the direct agglutination with blocking antibodies is vague and is entirely disproved by the fact that albumin-suspended cells are also active (Diamond, L. K., and Denton, R. L.: *J. Lab. & Clin. Med.* 30:821, 1945). In the light of these facts, the term "conglutination" should be limited strictly to the phenomenon described by Bordet and Gay (Bordet, J., and Gay, F. P.: *Ann. Inst. Pasteur* 20:467, 1906), a phenomenon in beef blood dependent on a heat-labile component. The use of the term "conglutination" for the direct reaction of serum, which was criticized also by British workers (Coombs, R. R. A.; Mourant, A. E., and Race, R. R.: *Brit. J. Exper. Path.* 26:255, 1945) should be abolished. Actually, albumin-suspended cells are far more sensitive, and are therefore preferable (Levine, P.: Unpublished data).

DR. JOSEPH H. GLOBUS: In order to establish that a lesion exists in the brain when a vessel is occluded, it is necessary to demonstrate the existence of reactive phenomenon around that vessel. The brain is sensitive to occlusion of blood vessels, and when a vessel is occluded there is an immediate reaction around the vessel, expressed in accumulation of such elements as glial cells and macrophages. In the material presented here, I saw no evidence of reactive phenomena, and in their absence I cannot accept the fact that this occlusion of blood vessels has been actually demonstrated and that it played a part in the development of lesions which have not been demonstrated.

My associates and I have in our collection 6 cases of erythroblastosis. We have grouped them with the cases of kernicterus, but we noted that the icteric discoloration was not limited to the basal ganglia, but that the gray matter wherever it was found was affected in varying degrees. It is true that the gray matter on the surface of the brain was not affected as much as the basal ganglia, the inferior olives, the red nucleus or the gray matter of the cerebellum; but it is certain that this discoloration, this accumulation of pigment, was not limited to the basal ganglia. It was widespread, and cases were reported in which the gray matter of the spinal cord was equally affected. Moreover, in none of the 6 cases were neurologic manifestations exhibited in the nature of meningeal irritation or involvement of the cortex or basal ganglia. No cerebral lesions of any kind were noted in these 6 cases.

DR. LEON H. CORNWALL: I wish to endorse what Dr. Globus has said regarding the absence of areas of degeneration around the thrombosed blood vessels. I saw no such areas in any of the photomicrographs.

I wish to ask one or two questions. First, is the term "kernicterus" a desirable one to retain in the nomenclature? Many have long felt that neurology should function as the supreme commissar of the hierarchy that presides over medical diagnosis and therapy. In order to exercise our acumen in diagnosing correctly the disease under discussion, we, as clinical neurologists, must possess a degree of serologic insight sufficient to enable us to evaluate such tests as conglutination, blocking and agglutination, in order to determine the presence or absence of the Rh factor in mothers of prospective infants. Dr. Brody has urged us to become more interested in this disease in order that we may contribute of our diagnostic and therapeutic skill in caring for these unfortunate infants. I am somewhat confused, as is Dr. Globus, as to just how we are to make our diagnoses. It is my

understanding, and I believe that Dr. Globus is in accord, that the diagnosis has up to now been made only after necropsy. Such a situation, of course, puts the diagnostic ability of clinical neurologists to a severe test.

If I understood Dr. Bródy correctly, he advised the removal of the offending isoimmune bodies by drainage. I do not know just how to do a venipuncture on an unborn infant.

For my second question, I want to inquire how he would suggest that we treat the erythroblastic infant prenatally after we have arrived at a diagnosis from serologic studies of the mother? Even more pertinent is the question how we are to arrange to have the mother come under our supervision in order that we may be enabled to treat her unborn offspring. All this should impress us with the rapid pace at which medicine is progressing.

DR. ALEXANDER S. WIENER: As I am not a neuropathologist, I must admit that some of the questions are too difficult for me to answer; I shall therefore confine my remarks to the serologic and clinical aspects. We have good evidence now that the placenta can act as a filter for separation of various sorts of antibodies, because it lets blocking (univalent) antibodies through, but not agglutinating (bivalent) antibodies. This explains the clinical observation that the severity of the disease in the infant (or fetus) is correlated with the maternal antibody titer in the case of univalent antibody disease, but not in the case of bivalent antibody disease.

While it is believed that the agglutinins are milked into the infant's circulation during labor as a result of increased intrauterine pressure, there is no evidence that cesarean section will prevent this. In fact, cesarean section opens the uterine blood sinuses and in this way may permit maternal blood to gain access to the fetal blood stream.

Dr. Levine pointed out that kernicterus can also occur when the maternal serum contains blocking antibodies only and asked how this may be explained. Such cases are exceptional, but we can now explain them. What happens in these cases is that the baby is born with its red cells coated with univalent antibodies. Fetal serum contains little or no conglutinin, but as soon as the baby is born the conglutinin begins to form. If the baby becomes extremely dehydrated and has a fever, the plasma proteins become more concentrated and aggregate to form conglutinin, and this conglutinin (colloidal aggregate of plasma proteins) is adsorbed by the sensitized red cells and causes the red cells to stick together. The resulting intravascular conglutination produces the same effects as intravascular agglutination. It may be, therefore, that in some cases kernicterus in the newborn can be prevented if the infant is not allowed to become dehydrated.

There is no way in which one can treat the fetus in utero, and we were misunderstood as to the use of exchange transfusion. That is to be performed on the infant as soon as it is born. To perform a satisfactory exchange transfusion, one must transfuse and simultaneously withdraw two or three times as much blood as the baby's entire body contains because after a while one is taking out some of the blood one is injecting. Of course, one cannot take out all the infant's blood at one time.

As for the cases of athetosis and dystonia in which there is no history of neonatal jaundice, Dr. Bakwin and I have found the normal percentage of Rh-negative mothers and none of these were sensitized to the Rh factor. Thus, in these cases the disturbance is not due to isosensitization; the clinical histories suggest, instead, that birth injury may be the pathogenic agent.

I have not time enough to cover the rest of the points, for which I am glad, because some of the questions were too difficult.

DR. MATTHEW BRODY: One of the tough problems we have to explain is the absence of kernicterus in infants with congenital atresia of the bile duct, in whom the jaundice is intense. It is true that there is little reactive change to the lesions we demonstrated tonight. However, we have seen these lesions in 4 fatal cases in which the child's mother showed large amounts of agglutinins. In various cases

these lesions can be demonstrated in every organ of the body: the brain, the lungs, the intestine and the kidneys. We feel that this structural change must be correlated with the serologic findings.

Dr. Globus pointed out that he was unable to demonstrate neurologic signs or cerebral lesions in the 6 cases he studied. I do not know whether or not the infants died of neurologic disease, but the mere fact that they had kernicterus and died is evidence that they died of something.

These vascular obstructions are not ordinary clots; they are agglutination thrombi, and they differ from ordinary clots, in which various mechanisms are involved.

The white matter is involved, but perhaps not so much as the gray matter.

Correlation of Clinical and Electroencephalographic Findings in a Large Series of Cases of Verified Cerebral Tumors. DR. PAUL F. A. HOEFER, DR. EDWARD B. SCHLESINGER (by invitation), DR. HARRY PENNES (by invitation) and MISS MARY D. COX (by invitation).

This paper was presented as a preliminary report on this investigation, a detailed presentation of which will appear in a future issue of the ARCHIVES.

DISCUSSION

DR. HANS STRAUSS: I cannot easily discuss this paper because I did not see it before its presentation and because the figures were projected so rapidly on the screen. I could record only one of these figures, namely, 67.5 per cent, which represented the authors' correct localization of hemispheric tumors. This compares with 68.3 per cent in similar material studied in the electroencephalographic laboratory of Dr. Wechsler's service at the Mount Sinai Hospital. It is gratifying to see that these figures are almost identical, though the methods in taking and evaluating the records vary. As a rule, my associates and I use eleven electrodes and rely for localization on measurements of the delta index (Strauss, H.: *Electroencephalographic Studies: A Method for Differential Diagnosis of Abnormal Electroencephalograms*, *J. Mt. Sinai Hosp.* 9:17-22, 1942) rather than on triangulation. In view of our almost identical results, I wonder whether for practical diagnostic purposes the authors needed to use so many electrodes.

Our surveys show at present 253 verified intracranial tumors, 164 of which are tumors of the cerebral hemispheres; the latter include 47 meningiomas and 117 gliogenous and metastatic tumors. In contradistinction to Dr. Hoefler's survey, we include among our tumors only true neoplasms, and not such lesions as subdural hematoma and cerebral abscess. Normal records were obtained in 63 cases, which represent approximately 25 per cent of all the intracranial tumors. However, the percentage of normal records varied greatly with the type and localization of the tumor. Normal records were obtained with about 80 per cent of the cerebello-pontile angle tumors and with only 12 per cent of the hemispheric tumors. Among the latter, there was a significant difference between meningiomatous tumors, with 23.5 per cent of which normal records were obtained, and gliogenous and metastatic tumors, with approximately 7 per cent of which the records were normal. A correct localization was made in 62 per cent of the meningiomatous and in 72 per cent of the other tumors. The difference in the number of normal records and correct localizations in the two series can be explained by the larger degree of electroencephalographic abnormality associated with tumors of faster growth. The gliogenous and metastatic tumors as a rule interfere more seriously with the metabolic function of cerebral tissue and so create a much higher degree of abnormality in the electroencephalogram.

In a previous paper (*J. Mt. Sinai Hosp.* 9:17-22, 1942) I classified the electroencephalograms according to the degree of abnormality on the basis of certain standard measurements. According to such standards, the degree of abnormality was high in 30 per cent of the meningiomatous tumors and in 71 per cent of the gliogenous and metastatic tumors. In a paper published with Dr. Greenstein (Greenstein, L., and Strauss, H.: *Correlations Between the Electroencephalogram*

and the Histological Structure of Gliogenous and Metastatic Brain Tumors, *J. Mt. Sinai Hosp.* 12:874-877, 1945), we demonstrated a correlation between the histologic structure of metastatic and gliogenous tumors of the hemisphere, as studied in the neuropathologic laboratory of Dr. J. H. Globus, with the degree of abnormality of the encephalogram, as measured by the focal delta index. I wonder whether Dr. Hoefer has made similar observations.

Only if the electroencephalographic changes are correlated with the clinical findings are they of the greatest diagnostic value. Is it also Dr. Hoefer's experience that meningioma with jacksonian seizures is associated with normal records in a much higher percentage of cases than is meningioma without such seizures?

DR. LEO M. DAVIDOFF: Dr. Margaret Rheinberger and I began to use electroencephalography in the localization of cerebral tumors in 1938, and our total figures are about the same as the number of cases that Dr. Hoefer has presented. We have a little over 350 cases in which we have histologic verification of the lesion only. I shall not attempt to discuss the technical side of this problem. If Dr. Rheinberger wishes, she may do so. Aside from any interesting physiologic facts that may have been observed as a result of these studies, I should like to ask Dr. Hoefer what have been the practical, clinical results in the application of this method of investigation in the treatment of cerebral tumors. I can only cite from our experience as follows, and this may be significant. As I said, we started to use this method in 1938. During the first two years we worked with a triple pen writing apparatus, and we were feeling our way; so the first two years of our studies were perhaps less productive than the later years. Thus, in comparing our brain tumor material prior to 1940 with that after 1940, we have made the following observation: Before 1940, which means usually that we were without the help of electroencephalography, we felt it necessary to make air studies in 56 per cent of our cases of cerebral tumor before operation. Since 1940, and that takes us up to about nine or ten months ago, when we moved our laboratory to Montefiore Hospital, we have found it necessary to use air injections in only 21, as against 56, per cent, indicating that we have reduced our preoperative pneumoencephalographic studies by a very considerable percentage. From that point of view, we feel that, whatever physiologic facts we may learn from this method of investigation, we have at least one practical result, that is, that we can spare a very considerable number of our patients the discomfort, and even the danger, of pneumoencephalography.

DR. MARGARET RHEINBERGER: I cannot add much to what has been said. Both Dr. Hoefer's and Dr. Strauss's figures are much like ours. There is one question I should like to ask Dr. Hoefer: What is a false localizing sign? I do not think there is such a thing. No sign can be false if it is correctly interpreted. Only when one considers all indications of abnormality in any pattern (whether or not they appear where one would expect in correlation with a more obvious disturbance) and endeavors to evaluate each in relation to the others and to the pattern as a whole does one have, in my opinion, the background on which to base judgment as to the probable location, or possible locations, of a discrete lesion which could produce all the abnormalities observed. Our results do not contain any false localizations; otherwise, as I said, they are much like those of other workers.

DR. PAUL F. A. HOEFER: To answer Dr. Strauss's questions first: We had planned to present a number of clinical correlations but had to put it off because of the shortness of time and because we had not reviewed our entire clinical material. I do not fully agree with Dr. Strauss as to the significance of jacksonian seizures in cases of meningioma. We have seen a good number of cases; one was presented tonight. However, I was struck by the fact that the incidence of seizures was lower with the meningiomas and higher with the astrocytomas than we had expected.

In reply to Dr. Davidoff's question: The material presented tonight was seen between 1940 and 1943. In these years about two thirds of our patients had air studies. I do not know how figures compare for the more recent material.

Dr. Rheinberger asks, "What is a false localizing sign?" I believe the best definition I can give is this: It is focal activity conducted from its site of origin by long tracts or commissures to an area far removed from where the lesion actually is. It would mislead one if one were to look for the tumor in the area where the signs appear. If, as in the case of a cerebellar tumor or a tumor of the eighth nerve, the site of the original lesion is inaccessible to electroencephalographic study, the "false" signs may be the only localizing signs. In other instances, as in those of lesions of the temporal lobe, one can distinguish between the true focus and its "mirror" image on the opposite side. In a study conducted with Pool (Hoefer, P. F. A., and Pool, J. L.: Conduction of Cortical Impulses and Motor Management of Convulsive Seizures, *ARCH. NEUROL. & PSYCHIAT.* **50**:381-400 [Oct.] 1943), I was able to show a number of conduction mechanisms for cortical electrical activity, and this is the probable explanation for false localizations of cerebral tumors.

Book Reviews

Psychiatric Interviews with Children. Edited by Helen Leland Witmer. Price \$4.50. Pp. 443. New York: Commonwealth Fund, 1946.

Direct psychotherapy with children is a new field in psychiatry, enveloped in an abundance of theory, little standardized in its application, and therefore difficult for the student to grasp. This recent publication of the Commonwealth Fund, elucidating psychotherapeutic processes through detailed case records, will provide the worker in the field with real help in his effort to translate theoretic considerations into practice.

The editor, Helen Leland Witmer, has collected 10 case records from the files of eight experienced therapists, Frederick H. Allen, Phyllis Blanchard, Lydia M. G. Dawes, Hyman S. Lippman, Martha W. MacDonald, H. B. Moyle, Beata Rank and Robert A. Young. Each record describes in detail the progress of the therapeutic relationship, from the initial interview to the termination of treatment, with a brief follow-up study appended. Accompanying each record are footnotes by the therapist discussing the procedures followed and interpreting productions and behavior. In addition, there are intake and progress reports by the social worker who guides the mother throughout the period of the child's treatment. This direction for the parent is closely integrated with the psychiatrist's work with the child, and its importance in the total therapeutic process stands out clearly.

The 10 cases, classified under the headings "non-neurotic," "with neurotic symptoms" and "seriously neurotic," are fairly representative of child guidance clinic practice, although in two respects they are selected: In all cases either the home was intact or one parent at least was actively interested in the child, and in all cases treatment was successful. Common clinical problems are analyzed, including reading disability, feelings of inadequacy, sex identification, sibling rivalry, handling parental authority, the process of differentiation from parents and the severer anxiety states.

The editor prefaces the studies with an introduction to the subject of child guidance and "the dynamic of therapy." She provides in this section an excellent brief survey of the field, adding substantially to the importance of the volume.

The approach throughout the book is dynamic with various emphases, depending on the point of view of the individual therapist. In few cases is a rigid scheme set up, and generally the therapeutic relationship is used to provide a means of release for the child through play rather than through probing or explanation. Also, through joint action with the social worker the reality situation is at all times stressed.

The importance of these principles of technic as determinants of success of treatment emerges clearly in the case studies, but one other factor stands out in perhaps even stronger relief—the art of the therapist. Here, as in a few other writings, the personal quality of the therapeutic relationship is brought into sharp focus for the reader's analysis and study. It is this frank exposition of the art of psychotherapy that makes "Psychiatric Interviews with Children" an unusual and outstanding addition to the literature of child psychiatry and psychotherapy in general.

Mongolism and Cretinism: A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency. By Clemens E. Benda, M.D. Price, \$6.50. Pp. xv, plus 310, with 101 illustrations. New York: Grune & Stratton, Inc., 1946.

Cretinism has been one of the mysteries of abnormal development. Appearing in all races and in the "best" of families, it has puzzled physician and geneticist alike. Benda does the medical profession a great service in lifting the veil of this

mystery and in analyzing the disorder on the basis of some 300 cases personally observed at the Wrentham State School. Since mongolism and cretinism are often confused, he includes parallel studies on these two related disorders of the endocrine system, with clarification of the details of each. He reaches the conclusion that mongolism is due to hypofunction of the pituitary body and cretinism to hypofunction of the thyroid gland, and that the physical characteristics of mongolism, better termed acromicria, are the reverse of acromegaly. In order to accomplish this demonstration, he surveys the field with great thoroughness, basing his discussion on necropsies in 48 cases. The lesions in the pituitary body are striking, and are characterized as follows: "1. Deficiency of the gamma cell system and general inability of formation of chromophilic elements. 2. Chromophilic shift toward eosinophilia with absence or deficiency of gamma cells and pathology of beta cells. . . . Mongolism is the congenital type of hypopituitarism."

It has long been recognized that the pituitary gland is the "master gland" of the body, and that its various hormones stimulate the thyroid, adrenal glands, gonads and mammary glands, as well as performing other functions. When the pituitary gland is congenitally deficient, the child is unfinished, and this is apparent in most of the tissues of the body, including the brain. Benda includes also morphologic and chemical studies on the blood. The results of these are shown in numerous graphs and tables, but the observations are not outstanding and would not be of value in doubtful cases because of the overlapping of figures for the two diseases, mongolism and cretinism.

Mongolism, Benda shows conclusively, is determined by a disturbance in the maternal condition. Age; multiple births; ill health, particularly psychosomatic disorders; abortion; bleeding; threatened abortion, and prematurity appear with such frequency in the case histories as to indicate that when a mongolian idiot is born the mother is close to sterility. It is not yet possible to forecast the birth of a child with mongolism on the basis of any single factor, but when two or more are present the physician may be warranted in preparing the pregnant woman for bad news. The mongolian idiot is a "salvaged abortion," and not too much should be done to prevent a threatened abortion if several unfavorable factors are present in the maternal condition. As far as treatment is concerned, the mongolian idiot cannot be expected to achieve physical or mental maturity until some effective pituitary preparation is discovered. Thyrotropic hormone is promising, but most reliance is placed on thyroid substance because of its easy control. Poor heat regulation may contribute to the many infections that occur in mongolian idiots, so that attention to extra warmth and exercise and frequent feedings high in carbohydrate and salts and low in fats may be desirable.

Benda's monograph is detailed, specific and accompanied with many illustrations. The literature on mongolism is cited abundantly, with significant contributions on cretinism included. It is an outstanding contribution to the clarification of a disorder afflicting an estimated 60,000 inhabitants of the United States.

Textbook of Abnormal Psychology. By Carney Landis and M. Marjorie Bolles. Price, \$4.50. Pp. xi, plus 576. New York: The Macmillan Company, 1946.

The plan for presentation of the field of abnormal psychology in this volume differs from that in less recent textbooks in extending the range of content and in covering similar content from a multiple approach. Thus, one section is devoted to terms and concepts to be utilized in description and classification; another section is concerned with various diagnostic categories; still another, with various aspects of psychopathology without direct reference to their diagnostic category; several chapters elaborate general basic explanatory concepts, and, finally, contributions from the various sciences, from education and from the law are evaluated. The addition of chapters on medical psychology, the law and mental abnormality, and the role of the brain in psychopathology is particularly welcome. These

chapters summarize new material that is pertinent to the area of abnormal psychology.

Each chapter is systematically organized to cover the factual data; the history, and the physiologic, the analytic, the neurologic, the biologic and the psychologic experimentation and contribution, with the novel addition of a subjective description of a personal experience by a victim of the disorder whenever feasible. In addition to this meticulously systematic approach, the glossary, comprehensive index, chapter summaries and bibliographies make for ease of use by the student.

Proper emphasis is placed on the extent of unsolved problems in the abnormal field. However, the sheer quantity of painstaking summaries of experimental studies in the biologic, physiologic and neurologic fields, which have admittedly thrown all too little light on the basic problems, tends to water down the impression of positive values contributed by some of the more dynamic approaches.

This volume is recommended for use by students for its comprehensiveness and inclusion of valuable new material.

Chronic Disease and Psychological Invalidism: A Psychosomatic Study.

By Jurgen Ruesch, M.D., and collaborators. Published with the sponsorship of the American Society for Research in Psychosomatic Problems. Pp. 191. New York, 1946.

This monograph is the result of a study made at the Langley Porter Clinic by members of the Division of Psychiatry of the University of California Medical School, under a grant from the Office of Scientific Research and Development.

One hundred and eighty-seven patients were studied after referral from other hospital departments because of chronic disease, the physical symptoms of which had persisted for an undue length of time. All patients with psychoneuroses and psychoses without physical symptoms and with psychoneuroses which had never been treated for physical symptoms were excluded. One hundred and twenty-three of the patients were seen for a short period, and a complete medical work-up, psychiatric diagnosis, psychologic tests and evaluation of social class membership and cultural factors were made. The other 64 patients were studied intensively and subjected to individual and group psychotherapy, and information concerning their character structure was given special attention.

The results of these studies are reported in this monograph, both in statistical form and with regard to the dynamic factors involved. There is also a discussion of certain of the specific problems most frequently encountered, such as those of the frigid woman, venereal disease, abused operations, abuse of medicine, diets and rest, and the perpetually referred patient. An attempt is also made to determine the prognostic possibilities for treatment in 53 of the patients, especially with psychologic tests, and to relate these to the actual therapeutic results obtained, with a description of the therapeutic methods used. Finally, there is a stimulating discussion of the psychodynamic factors presented by these patients and the reciprocal relationships with the actual physical disease present, and a provocative attempt is made to correlate delayed recovery with social class membership and attitudes.

This monograph is a valuable addition to psychosomatic literature and can be read with profit by all physicians.

A Textbook of Psychiatric Nursing. Formerly entitled "A Textbook of Psychiatry." Fourth edition. By A. P. Noyes, M.D., and E. M. Hayden, A.B., R.N. Price, \$3. Pp. 396. New York: The Macmillan Company, 1946.

The authors, a psychiatrist and a psychiatric nurse, have changed the title of their latest edition because of an increased emphasis on nursing procedures in this, the fourth, edition. This title is apt to be misleading, since, except for the added chapter on nursing procedures, the emphasis is still chiefly on psychiatry. In the fourth edition the chapter on the development of the mind has been omitted, without destroying the value of the text. Discussion of the organic psychoses is now

confined to two chapters less than formerly but gives adequate consideration to the more common conditions.

Throughout the volume there is commendable emphasis on the thinking, feeling and behaving of human beings, rather than strictly on the investigation, diagnosis and treatment of psychiatric patients. The instructions to the nurse along the lines of the patient's thinking, feeling and behaving are too general. The chapter entitled "Principles of Psychiatric Nursing" is also too general, owing perhaps to the fact that so many subjects are included in a single chapter.

The basic principles of care incorporated in psychiatric procedures do not vary greatly. It is not very clearly brought out in this book, however, that changes in application, safety measures and equipment associated with these procedures will be found according to the location and physician. Nursing functions prior to and following the treatments discussed would make this book more valuable to students of nursing.

The organization and arrangement of the text follow lines of previous editions, which have proved satisfactory to a great degree. Affiliating nursing students have found this text very helpful, and the new edition should prove increasingly so.

There are a serviceable glossary and index. Some of the explanations of psychiatric terms fall short of clarity; e. g., "hysteria: a form of psychoneurosis producing various symptoms, many of which simulate physical disease" (page 379) and "extravert: one whose personality is characterized by extraversion" (page 378).

News and Comment

INTERNATIONAL CONFERENCE ON PSYCHOSURGERY

An international conference on psychosurgery will be held in Lisbon, Portugal, in April 1948, at the invitation of the Portuguese government and the University of Lisbon. Secretary of the United States Committee is Dr. Walter Freeman, 2014 R Street, N. W., Washington, D. C.

Archives of Neurology and Psychiatry

VOLUME 58

AUGUST 1947

NUMBER 2

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VASOSPASM ASSOCIATED WITH MULTIPLE SCLEROSIS

C. RAY FRANKLIN, M.D.

AND

RICHARD M. BRICKNER, M.D.

NEW YORK

EIGHTEEN patients with multiple sclerosis were observed to show constrictions of some of the retinal arterioles. Scotomas were usually associated with the constrictions, and sometimes there was also a reduction in visual acuity. In most instances in which they were employed, fast-acting vasodilating drugs caused prompt, temporary reduction of the constrictions and of the size of the scotomas (sometimes to zero), and in several instances an increase of visual acuity as well.

When sufficiently frequent observations could be made, many of the constrictions proved to be transient, appearing and disappearing over a period and often shifting from one vessel to another. Scotomas frequently were transient, too, disappearing from one part of the visual field and reappearing in another. The constrictions were interpreted as spasms.¹

PRELIMINARY OBSERVATIONS

CASE A.—The first case seen, that of a white man aged 30, was one of undiagnosed disease of the central nervous system. There was evidence of dissemination of lesions, but no definite diagnosis of multiple sclerosis or of any other condition could be made with assurance. In retrospect, multiple sclerosis may be the diagnosis. Nonetheless, this case became the starting point for the investigations to be reported, all the rest of which were made with patients who had ordinary, clinically indisputable multiple sclerosis.

Case A was studied in 1942 and 1943 by one of us (C. R. F.)² at the Neurological Institute of New York, in the service of Dr. Irving Pardee. Included in

This work was supported by the Fund for Research, Inc.

The ophthalmologic observations are Dr. Franklin's unless otherwise specified.

From the Neurological Institute of New York and the Neurological Service of the Mount Sinai Hospital.

Read at a meeting of the Inter-Hospital Conference of the New York State Department of Mental Hygiene, held at the New York Psychiatric Institute and Hospital, Sept. 11, 1946.

1. Brickner, R. M., and Franklin, C. R.: Visible Retinal Arteriolar Spasm Associated with Multiple Sclerosis: Preliminary Report, *Arch. Neurol. & Psychiat.* **51**:573 (June) 1944.

2. Franklin, C. R.: Presented at a meeting of the New York Academy of Medicine, Section of Ophthalmology in 1943.

the history were recurrent attacks of blindness of the left eye, lasting two to twenty-five minutes.

Fundi and Visual Fields.—On Jan. 15, 1943, while one of us (C. R. F.) was making rounds, the patient suddenly complained that his left eye was "closing." Ophthalmoscopic examination revealed the superior temporal artery to be a mere white streak. The venules in this region showed broken columns of blood, giving a box car appearance. This phenomenon lasted about three minutes, when the patient stated, "My eye has opened again and I can see." While the fundus was being observed, the arterioles gradually became pink; the color deepened progressively until the vessels appeared normal.

The vessels appeared normal in both eyes after the attack had passed. During the attack the left pupil measured about 5 mm. in diameter and did not react to light; the right pupil measured about 3 mm., and its reactions were normal. After the attack the pupils were of equal size, measuring about 3 mm.

At this time the papillas were objectively within normal limits, but later a comparative pallor of the temporal side of the left papilla was observed.

The visual fields, examined routinely on Dec. 22, 1942, had contained a rather large scotoma on the left when tested with 2 and 5 mm. test objects, while on the right a suggestion of contraction was found with a 2 mm. test object, both fields being taken at a distance of 1 meter. Reexamination on January 27 showed that the scotoma on the left had become greatly enlarged, and the right field showed a notch, homonymously placed.

For several years the patient continued to have similar attacks, always involving the left eye only. More recently slighter attacks have occurred in the right eye, according to the patient's reports. Attacks have sometimes been precipitated by either of two definite factors—sudden emotional tension or sudden exposure to bright light. For example, on one occasion the patient had been working in a tunnel for several hours; an attack occurred on his emerging into bright sunlight.

CASE B.—F. M., a white woman aged 30, was referred by Dr. Bernard Glueck in February 1944. She presented a typical picture of multiple sclerosis, only moderately advanced.

Among her complaints were attacks in which the vision of the right eye became blurred and "shimmering." These attacks were particularly prone to occur during hot baths.

Fundi and Visual Fields.—F. M. was observed during and directly after several hot baths. In each instance she stated that she was undergoing an attack. At these times the retinal arterioles of the right eye regularly revealed constrictive changes.

On the first examination, Feb. 28, 1944, while the patient was complaining of a spontaneous attack (not following a bath), the pupil of the right eye was dilated with neo-synephrine hydrochloride (10 per cent). Pronounced constriction of all the ordinarily visible retinal arterioles was found. The arterioles were the size of threads, some of them being practically colorless. Many of these constrictions changed as the examiner watched; each of the four main divisions of the central retinal artery independently became dilated and constricted again. The changes were manifested by alterations in color and size. This gave the fundus a continuously shifting, kaleidoscopic appearance. The vessels of the fundus of the left eye were normal. In later examinations, after hot baths, the findings were less spectacular. Segmented constrictions were seen in various arterioles at different times.

The visual fields were plotted several times, using the right eye, immediately on the emergence of the patient from immersion for eight to ten minutes in water at a temperature of about 98 F. Multiple, small scotomas were found each time (fig. 1 *B*). The patient would state that she was experiencing an attack. In about ten minutes the attacks began to fade and the arterioles to return to their normal state. Visual fields plotted during the period of fading showed coalescence of some of the scotomas and disappearance of others.

Visual fields plotted between attacks showed only slight variation in number and position of scotomas in this case, and in no instance did the number of scotomas even approach what was found during attacks (fig. 1 *A*).

SYSTEMATIC OBSERVATIONS

Since these initial observations were made, 21 patients with multiple sclerosis have been studied systematically. The 21 patients have been divided into three groups: group A (13 patients), made up of those with scotomas; group B (4 patients), composed of those who could not cooperate well enough for satisfactory testing of the visual fields but

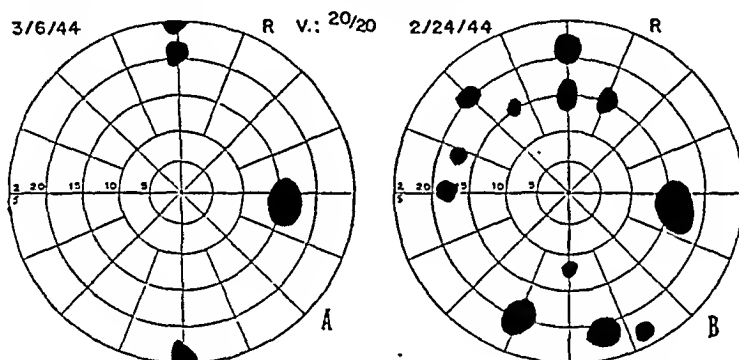


Fig. 1 (case B).—*A*, visual field in the right eye plotted between attacks with a 5 mm. test object at a distance of 1 meter. *B*, visual field in the right eye plotted immediately after the patient had been immersed in water at a temperature of about 98 F. for eight or ten minutes (5 mm. test object; distance 1 meter). The patient stated that she was experiencing an attack.

who had constrictions of retinal arterioles (these patients all had scotomas, although the latter could not be mapped out reliably), and group C (4 patients), comprised of those with no scotomas.

Experiments with vasodilating drugs were performed on 1 patient in group C and on 9 of the 13 patients in group A. (Of the 4 patients in group A not subjected to the drug tests, 1 (case 1) was incapacitated and could not come for the tests; 2 (cases 2 and 3) had no constrictions, and 1 (case 13) had scotomas which were too small to test. The last patient was subjected to another type of test however.

Most of the patients complained not only of dimness or blurring of vision, but of a "shimmering" (as in case B), which caused objects not only to shimmer but to be vaguer than normal in outline. Sometimes, in tests for visual fields the test object was said to "shimmer and fade."

TECHNIC OF EXAMINATION

Patients came to the office of one of us (C. R. F.), rested and then were subjected to an examination of the fundi and to plotting of the visual fields. (In cases A and B, all studies were performed at the Neurological Institute of New York.)

Examination of the Fundus.—Dilation of the pupils was not employed (except once in case B) because it might have altered the arteriolar conditions of the fundus and it was desired to avoid confusion of observations at this early stage of the studies.

Examination of the Visual Fields.—Fields were tested on a tangent screen with 2 and 5 mm. test objects, at a distance of 1 meter. Not more than two tests (before and after administration of drugs) were ever conducted in one day. Data on the visual fields of patients who could not cooperate adequately were not used; there were 4 such patients (group B), and only the observations on their fundi were incorporated in this report.

Determination of Visual Acuity.—Visual acuity was tested with correction when the acuity was less than 20/20. All reports of visual acuity in this paper include such corrections. Visual acuities were tested prior to the plotting of the fields, both before and after administration of drugs.

Administration of Drugs.—Amyl nitrite: Two or three whiffs were given. In no case were the general effects sufficiently disturbing to impair the patient's cooperation in the tests.

Papaverine Hydrochloride: A dose of 0.065 Gm. was administered by intravenous injection (in cases 7 and 9 the dose was 0.0325 Gm.). There were no general effects which impaired the cooperation of the patient.

Second Examination of Fundi and Visual Fields: After the administration of amyl nitrite the fundi were reexamined immediately. After the administration of papaverine hydrochloride the fundi were reexamined in two to three minutes. Reexamination of the visual fields was begun immediately after the second examination of the fundus.

THE FUNDI IN GROUP A (PATIENTS WITH SCOTOMAS)

The following types of arteriolar change were observed: A. Generalized narrowing of the whole arteriolar tree, with an arteriolar-venous ratio of less than 2 to 3. Generalized narrowing sometimes remained unchanged over a considerable period, but sometimes it varied; e. g., in case 12 it was less prominent than before in the left eye on June 29, 1944 (table 3).

B. Transient constriction of individual arterioles, in the presence of an otherwise normal arteriolar tree. Individual arterioles would be constricted at one observation and not at another. The constricted part of the vessel would appear much whiter than the rest. It would also be distinctly narrower than the adjoining parts of the vessel. The change was abrupt, both distally and proximally. Examples, seen in case 12, follow.

April 24, 1944 (during a "spontaneous" attack of impaired vision): Constriction of the right inferior temporal arteriole only was seen (generalized narrowing was present in this case, however).

May 26: No focal constrictions were observed on the right; constrictions of macular arterioles were seen on the left.

June 5: Constrictions of the right superior and inferior temporal arterioles and of the left macular arterioles were seen.

July 11: Constrictions of the right and left superior nasal arterioles only were observed.

Various Dates: Constrictions of the macular arterioles were seen on one or both sides.

Additional shifts, in this and in other cases, are recorded in table 3.

C. Alternating filling and emptying of an arteriole. This is an uncommon observation. It was seen in a left macular arteriole in case 6 on Sept. 19, 1944, and in case 17. The vessel would appear normal; suddenly it would become colorless, and then suddenly it would refill with blood. An identical phenomenon was seen in case 12 on June 16 (table 3, footnote). This alternation of events, which was repeated several times, occurred in rhythm with the pulse in cases 6 and 12, but it had its own slow, irregular rhythm in case 17. No evidence of glaucoma was found in either case.

D. Hourglass constriction. This was observed not uncommonly in one arteriole or another (table 3). The vessel was pinched and white at a given point and normal otherwise. Such constrictions were transient except in the right superior temporal arteriole in case 11; in this case an hourglass constriction was seen in the same place for over a year, although it was more prominent in the earlier observations than in the later ones. In addition, a fixed hourglass constriction was seen in the right superior nasal arteriole over a period of several months early in the same year; ultimately it disappeared. In case 7 an hourglass constriction of the superior nasal venule was observed twice.

E. Segmented constrictions. Broken columns of blood were seen in these vessels, with narrow, white areas between them. Distal to the constrictions the blood column was complete.

With all these types of constriction, the vessels were only rarely occluded completely. Blood could be seen in the vessel distal to the constriction. Complete closure was thought to have been observed only in cases A and B during the attacks.

The constrictions were seen usually in those parts of the vessels which lay on or near the papilla. There were exceptions (cases A, B and some others).

Some of the data suggested a tendency for the same vessel to be involved more than once, but the observations were not numerous enough to establish or negate the possibility finally. The most striking hint of it was the long-standing limitation of attacks to the left eye in case A, as stated previously.

Most commonly there was a frequent shifting of constrictions from one arteriole to another (table 3). An arteriole with a constriction on one day would be normal on another, and constrictions often were seen involving vessels which had been, and later were again, normal.

F. Pulsation of the whole arteriolar tree, independent of the constrictions, in rhythm with the pulse.

The arteriolar changes are recorded in full in table 3 and summarized in table 4.

It is unfortunate that, as a development of the war situation, we are unable to present photographs of the fundi. Dr. Sylvan Bloomfield, of the ophthalmologic service of the Mount Sinai Hospital, attempted to take pictures of transient constrictions (*B* of the classification). These were not in cases in which the constrictions were the most conspicuous, and the constrictions are not distinct enough in the photographs to warrant publication. Because of an unfortunate series of coincidences, facilities for photography were not available at times when hourglass, segmented or any conspicuous constrictions were seen. Paintings of some of the fundi were made by Mr. E. G. Bethke and Mr. Alfred Feinberg. Paintings prove nothing, but we are presenting one to illustrate segmented constrictions (*E* of classification; fig. 2).

SCOTOMAS

The scotomas sometimes showed considerable spontaneous variation in size and shift in position when the period of observation was prolonged. A scotoma present at one examination would be absent at the next, and a new one would be found in another position (figs. 1 and 3; table 3). This was noted often enough to warrant the suggestion that it may be characteristic of active multiple sclerosis. Often scotomas were multiple (figs. 1, 3, 4 and 5; table 3). Multiplicity of scotomas, like the other symptoms of the disease, is not rare in multiple sclerosis, although this was not appreciated until Lambert observed it.³

EFFECT OF DRUGS ON SCOTOMAS

Many scotomas were found to be reduced in size, or to be absent altogether, after the administration of amyl nitrite or of papaverine hydrochloride. Some scotomas, however, showed no change after administration of drugs.

Fixed and Transient Scotomas.—In case 12, during a period in which shifting and changing scotomas were recorded, a scotoma which remained fixed appeared on the left (fig. 3). It was a central scotoma, first detected as part of a larger, transient scotoma on May 26, 1944; it grew in size (June 5), merged with larger, transient scotomatous areas, was detectable again as an isolated scotoma on June 29, having become

3. Lambert, R. K.: Personal communication to the authors.

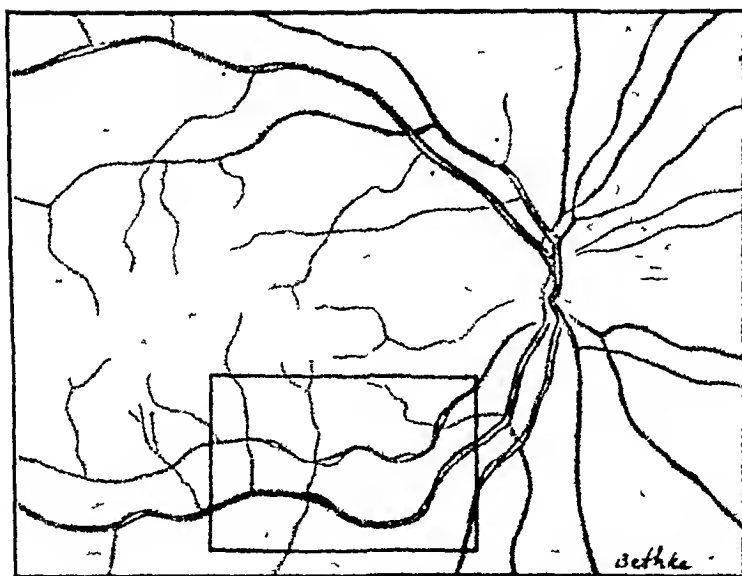


Fig. 2.—Retina in a case of multiple sclerosis in which the inferior temporal arteriole presents multiple segmented constrictions (*E* in classification in text) enclosed in the rectangle. In this picture, the constricted areas are shown as dark and the unstricted ones as light. This is due to highlighting by the light reflex of the unstricted areas during the artist's examination. More often the appearance was as described in the text, the constricted parts appearing lighter in color than elsewhere.

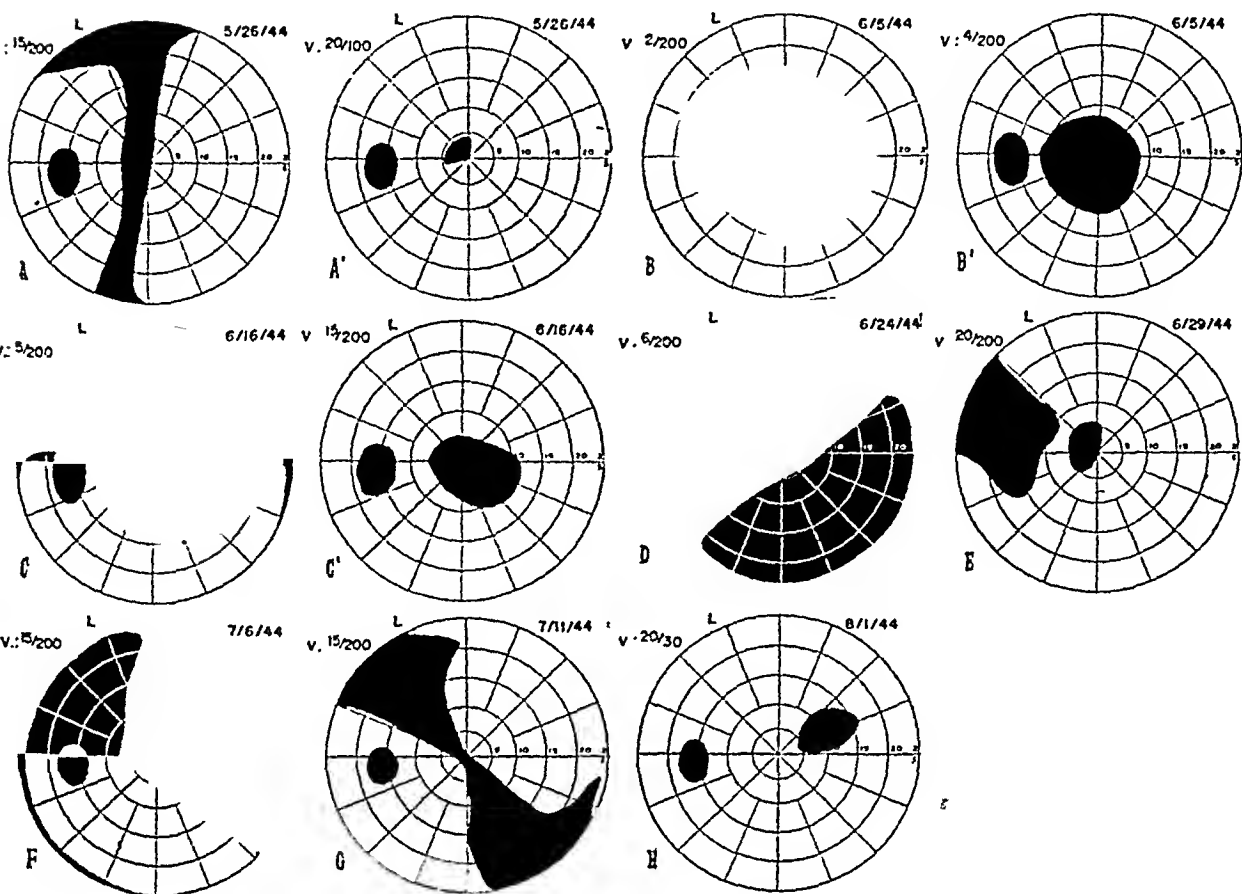


Fig. 3 (case 12).—Charts with plain letters represent a series of visual fields (left eye) plotted on various days. Charts with prime numbers show fields taken after administration of drugs, on the same day as the charts with the corresponding plain letters (e. g., *A*, on May 26, 1944, before injection of the drug, and *A'*, on May 26, after administration of the drug). The fields in successive observations can be followed independently of the drug experiments by ignoring the charts with prime numbers.

Papaverine hydrochloride was the drug used in all three of these experiments.

A 20 mm. test object was used at a distance of 1 meter except on May 26, when a 5 mm. test object was used.

The drug experiments (charts *A* and *A'*; *B* and *B'*; *C* and *C'*) show a striking reduction in the size of the scotoma following administration of the drug.

The sequential observations made on fields without drugs (charts *A*, *B*, *C*, *D*, *E*, *F*, *G* and *H*) show shifting of the position and change in size of the scotoma.

During a period when shifting and changing scotomas were recorded, a scotoma which remained fixed appeared on the left. It was a central scotoma, first detected as part of a larger, transient scotoma, on May 26; it grew in size (June 5), merged with larger, transient scotomatous areas, was detectable again as an isolated scotoma on June 29, having become reduced in size, and was last observed as part of another larger, transient scotoma on July 11. The identity and state of fixity of this central scotoma during the period when it was merged with larger scotomatous areas are shown by the effect of injections of papaverine hydrochloride. The larger areas, the transient nature of which was shown by their constant shifting of position and change in size, were caused by the drug to disappear, but the central scotoma remained. In fact, the central scotoma could be demonstrated as having its own independent existence at that time only by obliterating the transient scotomatous area with the drug.

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It might be conjectured that the central scotoma remained demonstrable because the drug was only partially effective and that a larger dose, or a more potent drug, might have caused its obliteration too. This is unlikely because of the constancy of the results, and particularly because on June 29 the central scotoma was demonstrated alone, without the preliminary employment of an injected drug. The patient had been taking large doses of papaverine hydrochloride by mouth, to be sure, but the same dosage had been maintained through July 6, on which date a larger scotomatous area had appeared, nonetheless.

Similar fixed scotomatous areas in company with transient ones were demonstrated in other cases as well. In case 6 there were a peripheral scotoma on the left and bilaterally enlarged blindspots on Sept. 19, 1944; only the peripheral scotoma was affected by amyl nitrite; on September 22 there was no peripheral scotoma but the blindspots were still enlarged, though smaller than on September 19. On September 28 the fields were normal (fig. 4). In case 9 there were a paracentral and two peripheral scotomas on the right on July 6, 7 and 8, 1944. The paracentral scotoma disappeared after the administration of drugs on July 7 and 8, while only one of the peripheral scotomas was affected. Reexamination on May 24, 1945 showed no paracentral scotoma; one peripheral scotoma was also gone (the one which had been affected by the drugs), while the other was smaller but was still represented vestigially. Case 5 provided an instance of an isolated, not very large, central scotoma, in which the center of the scotoma was fixed, while its peripheral part was transient and affected by the drugs. On June 23, 1944 the scotoma was reduced in size by amyl nitrite; on June 30 the scotoma was slightly smaller than it had been after administration of the amyl nitrite on June 23. Its peripheral, drug-affected part had disappeared, leaving the fixed core, which had been unaffected by the drug (fig. 5).

In addition, some scotomas were altogether unaffected by the drugs, as has been mentioned. In some instances (case 9, for example) in which a series of observations were made on serial days, one scotoma was persistently noted, and each time this was the one which remained

unaffected by the drugs. These phenomena are of interest in suggesting the existence of two distinct types of scotoma, the scotoma which is transient and affected by vasodilating drugs, and the scotoma which is fixed and unaffected by drugs.

EFFECTS OF ADMINISTRATION OF DRUGS ON BLOOD VESSELS

The inhalation of amyl nitrite almost uniformly produced general retinal vasodilatation. The constricted areas usually showed dilatation, but often it was less in degree than the rest of the vascular tree. In some instances the constriction disappeared altogether, whereas in others it was unaffected.

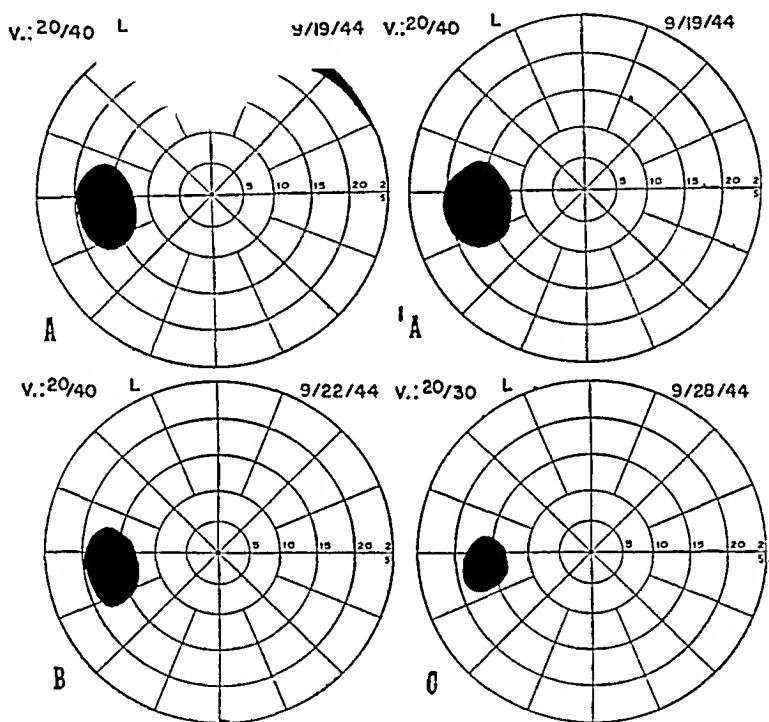


Fig. 4 (case 6).—Charts *A*, *B* and *C* represent a series of three visual fields (left eye) taken without drugs. Chart *A'* shows disappearance of the peripheral scotoma of chart *A* after administration of amyl nitrite, on Sept. 19, 1944.

The peripheral scotoma was not demonstrable on September 22 or 28. It is considered a transient scotoma, which can be affected by vasodilating drugs and which is the result of vasospasm without a fixed lesion. The enlarged blindspot, on the contrary, was not reduced in size by the amyl nitrite; if anything, it became slightly larger (paradoxical reaction of arterioles [?]; see text). In the subsequent observations, the size of the blindspot was found to be progressively smaller. The enlarged blindspot is considered a fixed lesion, the result of previous constrictions of greater intensity and/or longer duration than those responsible for the peripheral scotoma of September 19. The progressive reduction in size is not considered to be a consequence of vasodilatation but is thought to result from the healing processes of the tissue itself (5 mm. test object; distance, 1 meter).

The intravenous injections of papaverine hydrochloride sometimes appeared to produce general vasodilation also, and sometimes not. The vasodilation was less pronounced after papaverine hydrochloride than after amyl nitrite. The effect on constrictions, however, appeared quite similar to that of amyl nitrite.

The effects are summarized in terms of complete, partial or no relief of the constriction (table 3). In 18 trials with amyl nitrite, there were 4 instances of complete relief, 8 of partial relief and 7 of no effect. With papaverine hydrochloride, there were 4 instances of complete relief, 4 of partial relief and 7 of no effect.

A curious paradoxical effect was seen three times in case 11 and probably once in case 12. In case 11 the fixed hourglass constriction in the right superior temporal arteriole, instead of being reduced, extended distally along the vessel for a short distance after the inhalation of amyl nitrite (June 2 and 15, 1944). On earlier occasions, when this patient was in the Neurological Institute, similar effects on this constriction were observed after inhalation of amyl nitrite and after inhalation of carbon dioxide; at that time the patient had a similar hourglass constriction in the right superior nasal arteriole, seen regularly over a considerable period; and this constriction also extended along

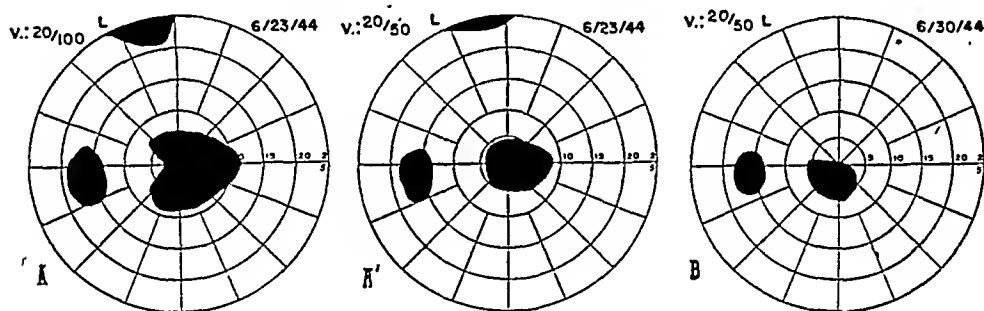


Fig. 5 (case 5).—Charts *A* and *B* represent two successive plottings of the visual field (left eye) on June 23 and 30, 1944, without drugs. *A'* shows reduction in size of the peripheral and central scotomas and a slight reduction of the slightly enlarged blindspot following administration of amyl nitrite, on June 23, 1944; the visual acuity also changed, from 20/100 to 20/50. On June 30 the peripheral scotoma was gone, and the central one was smaller; the slightly enlarged blindspot had become normal. Each of the three abnormalities is considered to represent a fixed lesion together with a transient disturbance, because each was partly unaffected and partly affected by the drug. It is considered that healing of tissues themselves occurred in the week between June 23 and June 30 in all three lesions—incomplete for the central scotoma and complete for the other two defects (5 mm. test object; distance, 1 meter).

the vessel after inhalations of the same substances. On June 2 the left macular arterioles, and on June 17 the left superior nasal arterioles, showed segmented constrictions after, but not before, the inhalation of amyl nitrite (not associated with changes in the visual fields; table 3, footnotes).

The probable paradoxical effect seen in case 12 occurred on May 26, when, after an injection of papaverine hydrochloride, a constriction which had not been present before appeared in the right inferior temporal arteriole. In this instance a peripheral scotoma at the top of the right visual field grew larger. Some doubt exists as to the

paradoxical nature of this observation, however, inasmuch as fifty minutes elapsed between injection of the drug and the second examination. In all other instances reexamination began within two or three minutes after administration of the drug. The fifty minute interval may have been sufficient for the new constriction to occur. (Despite this constriction, visual acuity improved slightly on the right [table 1]; it improved markedly on the left, where only a small central scotoma remained, no longer covering both sides of the point of fixation [fig. 3; table 1]).

EFFECT OF ORALLY ADMINISTERED MEDICAMENTS

No clearcut and indisputable effect on either scotomas or vascular constrictions was observed as a result of orally administered papaverine hydrochloride and other vasodilating drugs. The existence of spontaneous remissions in multiple sclerosis makes this problem difficult of approach in this manner.

EFFECT OF VARYING DOSES OF INTRAVENOUSLY ADMINISTERED PAPAVERINE HYDROCHLORIDE

As previously stated, the dose of papaverine hydrochloride employed in the experiments was 0.0325 or 0.065 Gm. The results were the same regardless of which dose was used. Differences might well be discovered in a larger series.

EFFECTS OF ADMINISTRATION OF DRUGS ON VISUAL ACUITY

Among the most striking observations were notable improvements in visual acuity immediately after the administration of the drugs in cases 5, 11 and 12. These changes are summarized in table 1 and further recorded in table 3.

The improvements in visual acuity in observations 1, 6, 7 and 8 coincide with reductions in size of central scotomas, or of large, bizarre scotomas which included central ones; in each of these instances the central part of the scotoma was included in the portion which became smaller after the administration of the drug (figs. 3 and 5). The improvement in observation 2 may perhaps be explained by the disappearance of the two small paracentral scotomas. In observation 4, many areas were involved in the spontaneous attack; those nearest the center had disappeared four hours later, when the second test was made. Observations 3 and 5 cannot be explained by the visual fields as recorded (table 3); they may possibly be accounted for by the disappearance of the shimmering vision, of which these patients, among others, complained.

In other cases no improvement in visual acuity followed administration of the drug.

CONSISTENCY AND INCONSISTENCY OF OBSERVATIONS ON
THE VISUAL FIELDS AND FUNDI

In assessing the consistency of the positions of the constrictions with those of the scotomas, the following factors must be given attention: consistency in position before with that after administration of drugs; consistency in the course of repeated observations in a given case; consistency of visual acuity with scotomas and consistency of changes in one with those in the other after administration of drugs.

TABLE 1.—*Improvement in Visual Acuity Following Administration of Amyl Nitrite and Papaverine Hydrochloride*

Observation	Case No.	Date	Eye	Visual Acuity			Scotomas; Same Drug	
				Before		After Drug	Before	After
				Amyl Nitrite	Papaverine			
1	5	6/23/44	OS	20/100	20/50	1 peripheral; 1 central	Both much smaller *
2	11	6/ 2/44	OD	20/40	20/30	Enlarged blindspot; 2 paracentral; 3 peripheral	2 paracentral scotomas disappeared
3	..	6/15/44	OD	20/40	20/30	Enlarged blindspot; 3 peripheral	1 peripheral scotoma disappeared
4	12	4/24/44	OS	20/40 (spontaneous attack)	20/20 (spontaneous recovery)	See table 3	
5	..	5/26/44	OD	20/30	20/20	1 peripheral	Enlarged blindspot †
6	OS	15/200	20/100	Bizarre, included central scotoma	Only small central scotoma remained
7	..	6/ 5/44	OS	2/200	4/200	Large central scotoma	Grew smaller †
8	..	6/16/44	OS	5/200	15/200	Bizarre, included central scotoma	Only smaller central scotoma remained †

* See figure 5.

† See figure 3. Note that on May 20 a fifty minute interval elapsed between the administration of papaverine hydrochloride and the second examination.

Consistency is not as simple to define as might be expected. A constriction in an inferior nasal arteriole is probably compatible with a scotoma in the superior temporal part of the field, or in the middle portion of the superior field if the constriction involves the main arteriole near its point of origin. However, if the constriction is in a small branch of a main vessel and the scotoma is a very large one, then the scotoma is probably only partly explained by the constriction. Constrictions in small branches might produce more extensive changes if produced on the background of general narrowing than if produced alone. Involvement of any one of several arterioles may cause enlargement of the blindspots. A constriction may permit the passage of

enough blood, and fast enough, so that there are no changes in the visual field. A scotoma may have resulted from a fixed lesion and be permanent in the absence of constrictions at the time of examination. The condition of the arterioles may change between the time of examination of the fundus and that of completion of the field tests (in case B they changed kaleidoscopically during the ophthalmoscopic examination). Some constrictions may have been overlooked. Some of the scotomas may have been caused by occlusion of a branch arising from the constricted wall of a larger vessel, instead of directly by partial occlusion of the vessel actually showing the constriction (see section entitled "Hypothesis That the Spasms Cause the Scotomas").

In actually making the evaluations, some of these factors presented themselves more frequently and conspicuously than others. A scotoma in an incompatible position was not considered necessarily inconsistent because, as previously stated, it might have been a fixed lesion, the result of previous constrictions. This was shown to be the fact several

TABLE 2.—*Consistency of Observations on Visual Fields with Fundi*

	Before Drugs		After Drugs	
	Number of Observations	Percentage	Number of Observations	Percentage
Consistent.....	70	57	21	50
Partly consistent.....	30	24	6	14
Inconsistent.....	20	16	15	35
Questionably consistent.....	3	2.4	0	0

times in cases observed repeatedly (page 129 and table 3). However, the absence of a scotoma where there should have been one was considered an inconsistency, despite the possible explanations described in the preceding paragraph. Large scotomas, probably too large to be completely explained by the constriction which was observed, but nonetheless partly explained by it, were considered partly consistent; it should be noted that this does not imply any inconsistency. Enlarged blindspots were considered consistent with constrictions in several different vessels. Central scotomas were deemed consistent with constrictions of the macular vessels; constrictions of those vessels without a central scotoma were called inconsistent.

The consistencies and inconsistencies are listed in table 2.

The general course of the scotomas and the constrictions was consistent over a period in the 4 cases in which four or more serial observations were made (cases 9, 10, 11 and 12). In general, scotomas and constrictions became more pronounced or less pronounced concomitantly (table 3).

TABLE 3.—Observations in Twenty-One Cases of Multiple Sclerosis *

Case	Age	Sex	Eye	Date	Scotomas					Fundl										Consistency	Visual Acuity		Shift- ing Seco- toma	Shift- ing Con- striction																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
					Central	Paracentral	Peripheral	Enlarged Blindspot	Contracted Field	Effect of Drug Amyl Papa- Nitrite verine	N	Gen	SN	IN	ST	IT	Mac	Pul	Effect of Drug		TP																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
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TABLE 3.—Observations in Twenty-One Cases of Multiple Sclerosis*—Continued

Case	Age	Sex	Eye	Date	Scotomas					Fundl										Consistency		Visual Acuity		Shift- ing Sco- toma striction	Shift- ing Sco- toma striction	
					Normal Field	Central	Paracentral	Peripheral	Enlarged Blindspot	Contracted Blindspot	Effect of Drug		N	Gen	SN	IN	ST	IT	Mae	Pul	Effect of Drug		Before Drug			After Drug
											Amyl Nitrite	Papa- verine									Pul	Cons				
12	30	F	z	4/24/44	++	++	+	+	+	+	P	..	20/40 20/40	z
			o	4/24/44	SM SM	+	+	20/40 20/20	++	++
			OS	5/20/44	..	Δ	..	+	+	++	c -1, C2	+	+	..	20/30 15/200	20/20 20/100	..	+
			OD	6/5/44	..	Huge	..	+	+	+	+	++	?	..	-1, C2	+	+	P	20/30 20/30	20/30 4/200	..	++
			OS	6/10/44	..	Δ	..	+	+	-	+	+	..	20/30 15/200	20/30 15/200	+	++
			OD	6/21/44	..	Δ	..	+	+	20/30 6/200	+	+
			OD	6/20/44	+	+	P	+	-	..	20/30	++
			OS	7/6/44	..	+	..	+	+	L	+	P++PL	+	P	..	20/200	+
			OS	Δ	+	+	S S P P	+	P	..	15/200	+	+
			OD	7/11/44	+	..	+	+	+	-	..	20/20	+
			OS	..	↔	+	+	+	P	..	12/200	+	++
			OD	8/1/44	+	..	+	+	+	+	+	..	20/20 20/30	+
			OD	10/3/44	+	..	R	+	+	?	?	+	..	20/20 20/30	+
			OD	2/19/45	+	+	+	+	+	+	..	20/20
			OS	+	..	+	+	P	..	+	+	+	..	20/20	+	..
			OD	2/26/45	+	+	+	P	P	+	-	20/20	++
			OS	R	++	..	+	+	P	+	P	20/30	+	+
			OD	3/3/45	+	..	+	+	+	+	-	20/20
			OS	R	++	..	+	+	P	+	+	P	20/30

[illegible]

TABLE 3.—Observations in Twenty-One Cases of Multiple Sclerosis *—Continued

Case	Age	Sex	Eye	Date	Scotomas										Fundl										Consistency		Visual Acuity		Shift- ing Con- striction		
					Normal Field	Central	Paracentral	Peripheral	Enlarged Blindspot	Contracted Blindspot	Effect of Drug		N	Gen	SN	IN	ST	IT	Mac	Pul	Effect of Drug		TP	Before Drug	After Drug	Before Drug	After Drug				
											Amyl Nitrite	Papa- verine									Pul	Cons									
15	20	F	OD	3/12/40	
			OS	3/12/40
			OD	3/15/40
			OS	3/15/40
			OD	3/21/40
			OS	3/21/40
16	37	F	OD	3/25/40	
			OS	3/25/40
			OD	4/9/40
			OS	4/9/40
			OD	4/12/40
			OS	4/12/40
17	33	F	OD	11/4/44	
			OS	11/4/44
			OD	11/10/44
			OS	11/10/44
			OD	5/25/45
			OS	5/25/45
18	37	F	OD	1/8/46	
			OS	1/8/46
			OD	1/22/46
			OS	1/22/46
			OD	1/22/46
			OS	1/22/46
19	33	F	OD	11/21/44	
			OS	11/21/44
			OD	11/21/44
			OS	11/21/44
			OD	11/21/44
			OS	11/21/44

		OD	11/24/44	H	H	H	++	P	+	..	20/200	20/200	..	+++
18	25	F	OD	4/24/44	+	+	..	20/200	20/200
			OS			+	..	20/200	20/200
			Group O			+	..	20/200	20/200
19	54	M	OD	3/7/44	+	+	..	20/200	20/200
			OS		+	+	..	20/200	20/200
20	37	M	OD	3/25/44	+	+	..	20/200	20/200
			OS		+	+	..	20/200	20/200
21	21	F	OD	8/17/44	+	+	..	20/200	20/200
			OS		+	+	..	20/200	20/200

A plus sign in any of the columns under "Scotoma" means that the indicated scotoma existed. The number of plus signs denotes the number of scotomas of that particular kind found in a given observation. R indicates relative scotoma; SM, a smaller scotoma; LGR, a larger scotoma.

* Under "Fundl," N means normal blood vessels; Gen, generalized narrowing; SN superior nasal arteriole; IN, inferior nasal arteriole; ST, superior temporal arteriole; IT, inferior temporal arteriole; MA, macular arterioles; Pul, pulsation; Cons, constrictions; TP, temporal pallor. Plus signs in the blood vessel columns under "Fundl" indicate presence of constrictions; S means segmented constriction; H, hourglass constriction; +, a constriction which was neither S nor H. P refers to the papilla; when symbols appear over the P, the constriction was on the papilla; when they appear under the P, the constriction was off the papilla; when they appear between two P's, the constriction was both on and off the papilla. L means a less pronounced constriction. The number of plus signs in the Mac column denotes how many macular arterioles were involved.

Each symbol stands for something separate; i.e., for case 12, 5/3/45, OS, "Peripheral" column, the + sign means a new peripheral scotoma, and LGR, enlargement of the old one, marked as smaller (SM) in previous observation (4/27/45).

In columns denoting the effects of drugs, — means no effect; P, partial relief; O, complete relief, and In, increase in size. Numbers in these columns refer to the box (box 1, 2, etc.) in which a positive effect was noted; the effect of the drug is denoted first, and then the box number.

In the columns "Shifting Scotoma" and "Shifting Constriction," the number of plus signs denotes the number of shifting scotomas or shifting constrictions.

† The superior nasal venule showed constriction (off papilla).

‡ One arteriole opened and closed, becoming alternating white and pink synchronously with the pulse. This vanished after administration of amyl nitrite. The vessel then merely pulsated.

† General retinal vasodilatation occurred, but was least at the arteriolar bifurcation at the lower pole of disk; a constriction was observed in this position (inferior temporal arteriole) three days later (11/24 in table).
NR means not recorded.

§ Complete relief of the two para-central scotomas; partial reduction of the two peripheral scotomas, one just above, and one just lateral to the blindspot; the other peripheral scotoma (top of field) and the enlarged blindspot were unchanged.

|| Generalized constriction, especially of the smaller arterioles.

‡ Extension of the hourglass constriction.

× The peripheral scotoma which increased in size was at the top of the field.

A efferential arteriole was present, contained a constriction and was pulsating.

** The macular arterioles showed segmented constrictions after, but not before, medication.

†† A new peripheral scotoma, near the top of the field, was completely relieved; other (old) peripheral scotomas, one at the top of the field and one lateral to the blindspot, were unchanged; the blindspot was unchanged.

— Not examined. ‡† Superior nasal arterioles showed segmented constrictions after administration of amyl nitrite, but not before. §§ All arterioles adjacent to the nasal side of the disk were constricted. ¶ The superior division of the central retinal arteriole presented an hourglass constriction.

z During spontaneous attack. ○ Attack subsiding, four hours later. △ Bizarre scotoma, including the central scotoma (fig. 3). □ Before drug administration in the right eye, the macular arterioles are greatly constricted. The nasal division of the superior nasal arteriole, by contrast with the temporal division, shows marked constriction; the nasal branch presents a whitish appearance for about 1 disk diameter. The three branches of the inferior division show moderate constriction; the most temporal is the most con-

stricted, alternately filling and closing with the pulse. In the left eye, the macular arterioles are in a constricted state. The superior temporal venule presents a dilated bulbous appearance where it crosses the arteriole, extending distally and proximally about 1 disk diameter. The inferior temporal arteriole shows a prominent constriction on the papilla (c) as it emerges from under the corresponding venule. After the intravenous injection of papaverine hydrochloride, the venules become so large and distended as to suggest varices. All the retinal arterioles dilate, but the areas of previously described constriction are still much in evidence. ¶¶ The part which remained was a small central scotoma (fig. 3). ⊕ Striking change in size and shape. ← → Two bizarre scotomas starting at the periphery and crossing the point of fixation.

> A hot drink was taken (usually tomato soup). < Segmented constrictions of the macular arterioles appeared, and the whole arteriolar tree became narrowed. ▲ A small peripheral scotoma, seen at other examinations but not on March 21 prior to the drink, appeared after the drink. ← General constriction of all the arterioles, most prominent in the left macular arterioles. ↓ Constriction in the medial division of the inferior temporal arteriole. ¶ During the examination, two divisions of the inferior temporal arteriole became greatly constricted, becoming practically colorless. * After the hot drink, pulsations included venules as well as arterioles. ● After the hot drink, the inferior temporal arterioles of the right eye each contained an area of constriction both on and off the papilla; the inferior temporal arteriole of the left eye contained an area of marked constriction about 2 disk diameters away from the papilla. ■ After the hot drink, the inferior temporal arteriole in the left eye contained a constricted area. ○ After the hot drink, the inferior temporal arteriole in the left eye was constricted in an area about 2 disk diameters away from the papilla. ◇ After the hot drink, two constricted areas were seen in the superior temporal arteriole of the left eye (one on and the other just off the papilla), and two branches of the inferior temporal arteriole showed segmented constrictions on and off the papilla.

Greatly decreased visual acuity was always associated with a central scotoma.

The consistencies and inconsistencies of changes in visual acuity with changes in scotomas are to be found in the data in table 1. Observations 1, 4, 6, 7 and 8 showed consistency, and observation 2 perhaps did. Observations 3 and 5 did not.

CONTROL OBSERVATIONS

There appeared to be no way in which to control the essential feature of these observations. Studies of patients with other diseases, whatever they showed, would not alter the basic hypothesis concerning multiple sclerosis which may be derived from these investigations. Hence, our full attention was devoted to cases of multiple sclerosis.

TABLE 4.—*Summary of Observations on Vasospasm and Scotoma in Twenty-One Cases of Multiple Sclerosis*

Observation	Number of Observations		
Hourglass constrictions.....	12		
Segmented constrictions			
Before drugs.....	10		
After drugs only.....	6		
Shifting scotomas.....	38		
Shifts in constrictions.....	77		
Constrictions affected by			
Amyl nitrite.....	9 (26%)	19 (54%)	7 (20%)
Papaverine hydrochloride.....	6 (33.3%)	6 (33.3%)	6 (33.3%)
Scotomas affected by			
Amyl nitrite.....	18 (46%)	10 (25%)	11 (28%)
Papaverine hydrochloride.....	5 (24%)	12 (57%)	4 (17%)

One feature which does require control relates to the matter of general change in blood flow. Are the shrinkages of the scotomas specifically related to the relaxations of the constrictions, or might the same result follow a mere general increase in blood flow to the impaired part? This question appears to be answered in favor of the first alternative by the fact that many scotomas did not become reduced in size after administration of a drug. The reader is referred to the previous discussion of fixed and transient scotomas in this connection.

A possible defect in this reasoning is that, while many of the scotomas appear to result from vasoconstrictive disturbances in the retina itself, some may depend on vasoconstrictive disturbances in other portions of the visual system. Supposedly, the same reasoning would apply to disturbances anywhere, but it is conceivable that it is applicable to the vasoconstriction in the retina alone and that the scotomas which did not respond to drugs may have arisen from vasoconstriction in other parts of the visual system, which might, perhaps, have some other sort of vascular arrangement.

Many other studies of many kinds obviously are indicated for the purpose of throwing more light on the effects of vasospasm in a variety of circumstances. From such sources, it may be possible to add to the understanding of the type of phenomena here described as occurring in multiple sclerosis.

The results of study for all cases described so far except those for cases A and B are recorded in table 3 and summarized in table 4.

ADDITIONAL OBSERVATIONS

THE EYES

Veins.—Attention should be called to case 6, in which the right superior nasal vein twice showed a constriction. This is in accord with the observations of Rucker.⁴

Acute Dilatation of a Vein.—An observation worthy of remark was made in case 12 on June 15, when some of the veins of the left retina became so large after an injection of papaverine hydrochloride that they gave the appearance of varicosities. These veins soon receded to their usual size, which was possibly slightly greater than normal.

Filling and Emptying.—The phenomenon of alternate filling and emptying of a single arteriole, noted in cases 6 and 12, was also seen in case 17 during a period in which the patient was at the Mount Sinai Hospital. The resident in neurology, Dr. Richard Drooz, and one of us (R. M. B.) examined her fundi, and each independently saw the left inferior nasal arteriole undergoing this process, exactly as described in cases 6 and 12 except that the rhythm was slow and irregular and not synchronous with that of the pulse.⁵ In 2 other instances (cases 13 and 14, table 3; footnote for June 11, 1945) the caliber of vessels was seen to change during the ophthalmoscopic examination.

Slight Changes in Advance of Overt Constriction.—In case 7, on Nov. 21, 1944, general retinal vasodilatation followed the inhalation of amyl nitrite. The dilatation was least noticeable at a place where an actual constriction was seen three days later (on November 24), although none had been observed there prior to the administration of the drug. Possibly slight constrictive changes, not visible under ordinary conditions, had begun to occur on November 21.

Diplopia.—Four cases with early or transient diplopia were observed.

CASE 2.—The patient had as one of her complaints diplopia on awakening every morning. It persisted for several hours and then disappeared. She was

4. Rucker, C. W.: Sheathing of the Retinal Veins in Multiple Sclerosis, J. A. M. A. **127**:970 (April 14) 1945.

5. Franklin, C. R., and Brickner, R. M.: Acute Alterable States in Multiple Sclerosis, Arch. Neurol. & Psychiat. **55**:418 (April) 1946.

seen on the morning of March 1, 1944, while the diplopia was present. Two whiffs of amyl nitrite were administered, and, according to the patient's subjective observation, the diplopia disappeared.

CASE C.—A white man aged 29 with early multiple sclerosis had as one of his symptoms morning diplopia in the right upper quadrant of his visual field. On April 24, 1945 the images were plotted. The patient was then given two whiffs of amyl nitrite. Immediate replotting of the fields showed that the diplopia had disappeared, the images now being superimposed. By June 27 the diplopia had

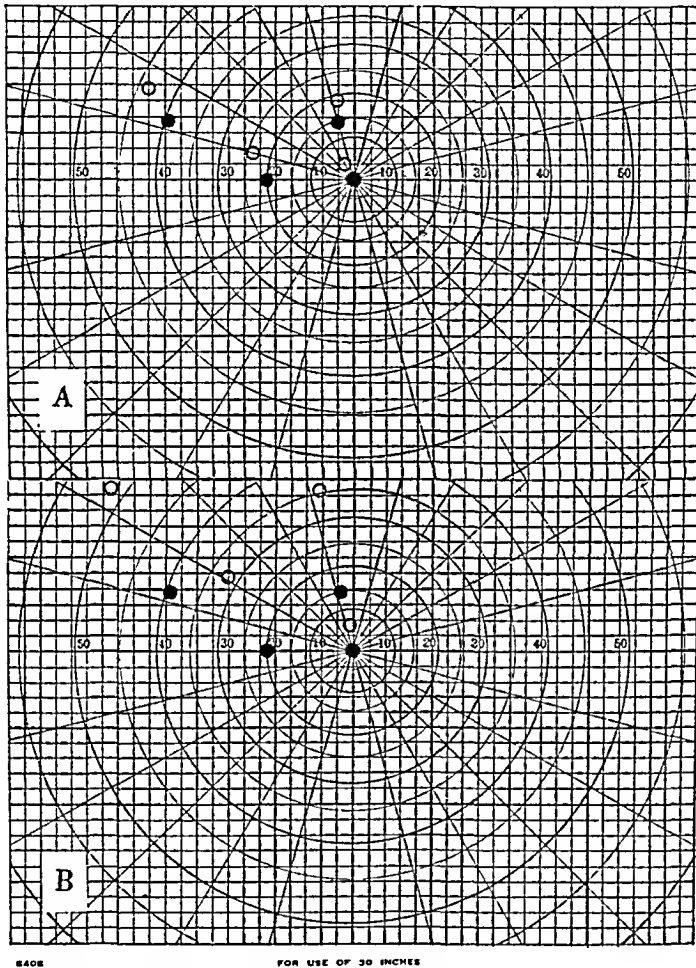


Fig. 6.—Improvement in diplopia following amyl nitrite in a patient with pronounced paresis of the left superior rectus muscle. *A*, before and *B*, after administration of amyl nitrite. Fields were taken at a distance of 30 inches (76 cm.), with red glass over the left eye. No diplopia was detected in any other part of the fields. The solid circles represent the real images; the rings, the false images.

increased in degree. Inhalation of amyl nitrite resulted in improvement, but not in disappearance, of the diplopia.

Mere decrease in the degree of diplopia, with some residual, fixed diplopia, may well be compared with the scotomas previously discussed, in which the drugs produced a reduction in size, leaving unaffected a fixed, residual scotoma. This comparison is especially pertinent in view of the earlier test in case C, in which

the diplopia was abolished completely (but transiently) with amyl nitrite. The hypothesis is suggested that the constrictions of vessels which produced the earlier diplopia finally resulted in a fixed lesion and that additional diplopia then developed as a consequence of additional vasoconstriction, which had not yet produced a fixed lesion. The fixed lesion showed itself as the residual, unaffected diplopia on June 27, and the new diplopia, not yet representing a fixed lesion, revealed itself as the component which was affected by the drug on that date.

CASE D.—A white woman aged 21, referred by Dr. Joseph Laval, was having her first attack of multiple sclerosis; the onset had occurred one week previously. She had had diplopia for three days. The patient was referred back to Dr. Laval, who plotted the diplopia before and after a subcutaneous injection of histamine diphosphate (0.001 Gm.) and found a decrease in the degree of diplopia following the administration of the drug.

CASE E.—A white girl of 18 years, referred by Dr. Ludwig Chiavacci, seen early in her second attack of multiple sclerosis, had had her first diplopia for two weeks. The symptom was due to extreme paresis of the left superior rectus muscle. Inhalation of three whiffs of amyl nitrite reduced the diplopia to about one-third its original range (fig. 6).

IMPAIRMENT OF VISION BY HEAT AND BY EATING

CASE 13.—A white man aged 42, a dentist, stated that his vision became impaired after drinking anything hot. He was examined several times immediately after drinking hot soup. Vision became impaired subjectively. On 6 of these occasions (counting each eye) constrictions were seen, although the vessels had presented a normal appearance before (table 3). No notable changes in the visual fields were detected, however; his small peripheral scotomas frequently became larger, but this was probably not sufficient to account for the subjective complaint. These slight changes in the fields were completely or partially consistent with the arteriolar changes in only 4 of 10 observations (counting each eye). No objective decrease in visual acuity occurred at all.

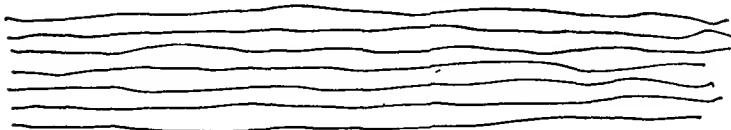
The patient also stated that the mere eating of food sometimes impaired his vision slightly.

CASE F.—A white woman aged 30 with multiple sclerosis informed us that she had occasionally experienced transient reduction and blurring of vision while under a hot hair dryer. This statement was not tested objectively.

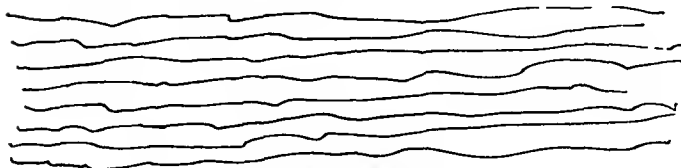
CASE 14.—The history was similar to that in case 13. Hot drinks, and the eating of food to a slighter degree, frequently increased the patient's chronic impairment of vision. The visual fields could not be adequately tested in this case either before or after the taking of the hot drink because of lack of cooperation. However, the changes in the retinal arterioles were striking (table 3). Arteriolar pulsation also increased, or appeared freshly, after the drinking in this case.

INTENTION TREMOR

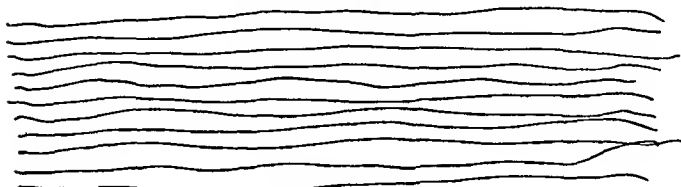
CASE 20.—A white man aged 35, a heavy drinker, had multiple sclerosis; included in his symptoms was a bilateral intention tremor, which had been present for an indeterminate period. He stated that the tremor usually became worse for a few minutes after smoking a cigaret, but only if he had been drinking steadily. If he had had no alcoholic liquor for two weeks, the cigaret had no effect on the tremor. On the other hand, he stated that four drinks in immediate association



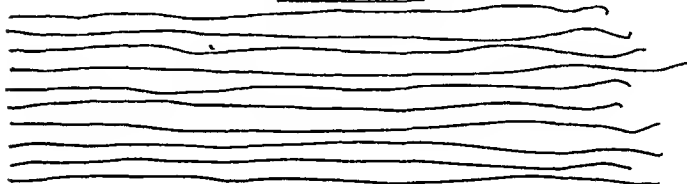
DIRECTLY AFTER SMOKING ONE CIGARET



ABOUT 3 MINUTES

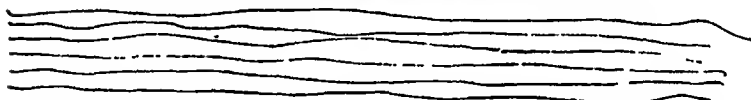


ABOUT 3 MINUTES

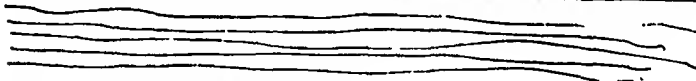


MAY 25, 1944 A.M. AFTER RESTING; BEFORE PROCEDURES

B



INTRAVENOUS INJECTION OF PAPAVERINE HYDROCHLORIDE 0.065 GM.; FAINTNESS



DIRECTLY AFTER SMOKING 1 CIGARET



ABOUT 2 MINUTES



Fig. 7 (case 20).—Intention tremor involving both upper extremities, illustrated for the right upper extremity by drawing lines. *A*, increase in the tremor following the smoking of a cigaret. *B*, prevention of the effect shown in *A* by preliminary injection of 0.065 Gm. of papaverine hydrochloride; after the injection, and also after the smoking, the tremor is the same as that before either procedure.

C

JUNE 8, 1944 10:00 A.M. AFTER RESTING: BEFORE PROCEDURES

[REDACTED]

DIRECTLY AFTER INTRAVENOUS INJECTION OF ISOTONIC SOLUTION OF SODIUM CHLORIDE, 4 CC., AND SMOKING ONE CIGARET

[REDACTED]

ABOUT 2 MINUTES

[REDACTED]

ABOUT 2 MINUTES

[REDACTED]

ABOUT 2 MINUTES

[REDACTED]

D

JUNE 2, 1944: 5 P.M. (3/4 PINT RYE WHISKY TAKEN BETWEEN 2:30 and 4 P.M.)
AFTER RESTING:

[REDACTED]

DIRECTLY AFTER SMOKING ONE CIGARET

[REDACTED]

ABOUT 3 MINUTES

[REDACTED]

C, control observation, with the injection of isotonic solution of sodium chloride. The increase in the tremor following the smoking of the cigaret is pronounced. D, effect of imbibing $\frac{3}{4}$ pint (375 cc.) of rye whisky before the test. The tremor is improved, and the smoking had no effect.

with the cigaret prevented the effect. The patient also stated that his imbalance of gait improved greatly when he was under the influence of liquor but that it was worse the day after.

Tests were conducted on the tremor and the manner in which smoking affected it. The patient, always after drinking steadily, would come to the office of one of us (R. M. B.), rest in a chair for half an hour and then demonstrate the tremor of the right upper extremity by drawing lines across a page with a fountain pen. He then smoked a cigaret, after which he resumed the drawing of lines (fig. 7 *A*). An immediate increase in tremor was apparent; subsequent series of lines drawn at one minute intervals showed a prompt waning of the effect until, in about five minutes, it was gone.

The effect was too transient to permit of attempts to relieve it with vasodilating drugs, but papaverine hydrochloride (0.0325 Gm.), introduced intravenously immediately before the smoking of the cigaret, prevented the increase in the tremor (fig. 7 *B*). There was no change in the tremor as a result of the procedure of injection. These tests were repeated many times. In a control test, in which isotonic solution of sodium chloride was administered instead of the papaverine hydrochloride which the patient thought he was receiving, the accentuation of the tremor occurred as usual after the cigaret (fig. 7 *C*).

Imbibition of 1 pint (500 cc.) of rye whisky just before the test not only prevented the effect of the cigaret but abolished the tremor altogether (fig. 7 *D*).

CASE G.—A white man aged 42 with multiple sclerosis also showed an increase in intention tremor on smoking a cigaret. Circumstances prevented his being tested with drugs.

LITERATURE ON RETINAL VASOCONSTRICTION

The literature on constrictions of the retinal arterioles is fairly large. It will not be reviewed here, since its only relevance to the present investigation is to show that constrictions have been seen by other observers, associated with many diseases, chiefly hypertension, arteriosclerosis and toxemia of pregnancy. In connection with the last-mentioned condition, it is worth remembering that pregnancy (not necessarily complicated by toxemia) often brings on or accentuates attacks of multiple sclerosis. Constrictions have also been observed in cases of Raynaud's disease and of thromboangiitis obliterans (Buerger's disease).

Apparently, constrictions of retinal arterioles associated with multiple sclerosis have not been reported by other authors. Rucker⁴ described and published photographs of hourglass constrictions in retinal veins in several cases of multiple sclerosis. In his cases no association with scotomas or other visual symptoms was reported and no tests with drugs were mentioned. Rucker⁴ also described sheathing of the veins in 34 cases in 21 of which the presence of multiple sclerosis was established and in 7 more of which that disease was suspected. We are able to confirm this observation. Rucker's studies and ours were conducted

independently, and we were unaware of his observations until some time after his report appeared.

Recently, Zeligs⁶ has stressed the importance of emotional tension in producing macular lesions in young Marines, supposedly on the basis of vasospasm. Such tension has a profound, precipitating effect in cases of multiple sclerosis, as has been pointed out by several observers (Brickner and Brill⁷). At least 1 patient in the present series (case A) described specifically his sudden attacks of unilateral blindness as sometimes resulting from sudden emotional tension.

There are a few reports of spasms with visual impairment in persons of ages ranging from 14 to 42 years without evidence of vascular disease or other known cause.⁸ Possibly these are related to our own observations. Although in none of the reported cases is multiple sclerosis said to have existed, we think it is pertinent to mention the possibility of this diagnosis. In Crisp's case^{8a} the attack followed a long automobile drive, something which has also been reported to occur in cases of multiple sclerosis. Pines^{8f} reported retinal vasospasm in "normal" young persons, but no studies of visual function were carried out.⁸

COMMENT

The plotting of visual fields is a subjective procedure, and it is always possible for errors to occur. We believe that our results are dependable because (1) the plotting was done by highly experienced testers, (2) the results were consistent, (3) the presence or absence of scotomas coincided almost uniformly with the patients' subjective experiences, (4) scotomas were consistent with visual acuities and (5) the tests were performed on highly cooperative, intelligent patients.

NATURE OF THE CONSTRICTIONS

The transient character of many of the constrictions suggests that they are spasms. They were present at one examination and absent, or

6. Zeligs, M. A.: Central Angiospastic Retinopathy: A Psychosomatic Study of Its Occurrence in Military Personnel, *Psychosom. Med.* **9**:110 (March-April) 1947.

7. Brickner, R. M., and Brill, N. Q.: Dietetic and Related Studies on Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **46**:16 (July) 1941.

8. (a) Crisp, W. H.: Spasm of the Retinal Arteries, *Am. J. Ophth.* **4**:188, 1921. (b) Halbertsma, K. T. A.: Un cas de spasme de l'artère centrale de la rétine, *Ann. d'ocul.* **163**:641, 1926. (c) Hairi, H.: Le spasme de l'artère centrale de rétine et l'obstruction consecutive de l'artère temporale inférieure, *ibid.* **163**:662, 1926. (d) Sédan, J., and Jayle, G.: Considérations sur les spasmes de l'artère centrale de la rétine, *Ann. d'ocul.* **173**:609, 1936. (e) Wagener, H. P.: Significance of Spasm in Retinal Arteriolar Disease and in Retinitis, *Tr. Pacific Coast Oto.-Ophth. Soc.* **24**:165, 1939. (f) Pines, N.: The Diagnostic and Clinical Value of Some Forms of Retinal Angio-Spasm, *Brit. J. Ophth.* **30**:470, 1946.

present in another arteriole, at another. Sometimes they appeared suddenly, as in cases A, B and 12, and disappeared in a few minutes. Moreover, some of them had an hourglass form. In case B constrictions fluctuated kaleidoscopically while being watched. Hereafter the constrictions will be referred to as spasms.

Narrowing of arterioles is an almost universal finding in association with atrophy of the optic nerve. This, however, is a generalized narrowing, involving all the arterioles. We have observed such general narrowing in some of the cases in this series, in some, but not in all, of which there was temporal pallor. There was evidence that general narrowing may sometimes be the result of spasms; it was decided, however, not to count it among the phenomena of spasm because the evidences were sparse and incomplete. Several factors distinguish the spasms we are reporting from this type of narrowing: (1) their involvement of single arterioles; (2) their presence in some instances without any temporal pallor which can be recognized, and (3) the factors mentioned in the preceding paragraphs—the transient character and the occasional hourglass form of the spasms and the continuous observed fluctuations in some cases.

There is some evidence in case 11 that fixed changes can occur in the walls of vessels as a result of spasm. The same constrictions were seen in the same positions for many months. The paradoxical reaction to vasodilating drugs also suggests a change of some kind in the structure of the vessel.

HYPOTHESIS THAT THE SPASMS CAUSE THE SCOTOMAS

The hypothesis that the reducible scotomas result from a reduction in blood supply caused by the spasms arises from the data, in view of (*a*) the coexistence of spasms and scotomas and the high level of consistency between them (table 2), and (*b*) the usually simultaneous effect on spasm and scotoma of vasodilating drugs.

Also supporting the hypothesis that the spasms may cause a sufficient reduction in blood flow to affect function are the 3 cases in which alternating emptying and filling of an arteriole were observed. No blood could be seen in the vessel during the empty phases, and the vessel could be identified at such times only by its blood-filled proximal portion. If such a condition were prolonged, function, as well as the metabolism of tissue, would by necessity be impaired.

Still further evidence that the spasms have an effect on visual function is found in the effect of the drugs on visual acuity in some cases.

It has already been mentioned that few spasms occlude the vessel completely. Almost always blood was visible in the vessel distal to the spasm, indicating that the scotoma cannot be the consequence of com-

plete deprivation of blood in that portion of the retina supplied directly by the vessel showing the spasm. It could mean (a) that localized portions of the retina are completely deprived of the blood coming from a branch of the arteriole showing the spasm, that branch arising from the spastic area and having its mouth occluded by the spasm in the wall of the parent vessel (fig. 8). This branch, being small and empty of blood, might not be visible on ophthalmoscopic examination. It could also mean (b) that the mere reduction of blood flow in the spastic vessel itself was sufficient to impair the function of that portion of the retina supplied directly by that vessel; (c) that the spasm disturbed the normal pulse of the blood in the distal part of the vessel, thus impairing the normal time relationships in the distribution of blood to tissue, and (d) that there was capillary collapse, due to locally reduced blood pressure.

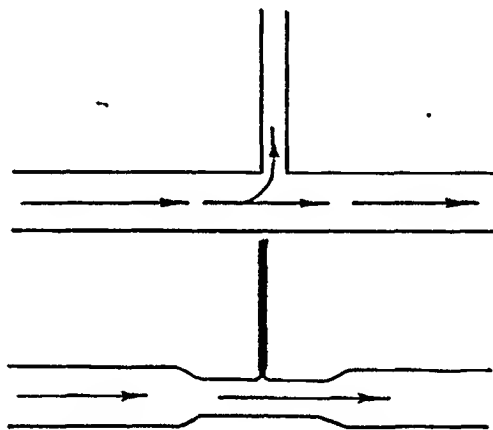


Fig. 8.—Diagram illustrating the hypothesis that small arterioles arising from a spastic, but not completely occluded, parent vessel may be completely occluded. The arrows indicate the direction of blood flow.

There are two weak links in the chain of evidence in support of this hypothesis. Although an explanation can be evoked for each of these objections they should be recognized as weaknesses at this point and be subjected to further observation. The first objection is that in some cases a reducible scotoma was in the wrong position to be explained by a given spasm. The other is that in these same instances there was, of course, no scotoma in the area indicated by the recognized spasm. The seemingly most reasonable explanations are given in the discussion on consistencies.

The rest of the accumulated evidence is sufficiently strong and consistent to warrant consideration of the hypothesis stated.

PULSATIONS

Pulsations of the entire arterial tree, synchronous with the rhythm of the cardiac pulse, were seen frequently, sometimes prior to and

sometimes after administration of the drug. No relation between pulsations and visual disturbances was found. None of the patients had glaucoma or cardiovascular disease. The pulsations are thought to reflect a change in vasomotor function which is not understood.

REVERSIBLE DISTURBANCE OF FUNCTION AND FIXED LESIONS

The rest of the discussion will be based on the hypothesis stated in the previous section.

The evidence suggests that two types of disturbances may, presumably, result from the spasms—one that is immediately reversible, in that it may be relieved by reduction of the spasm, and one not immediately reversible (fixed lesion). According to the hypothesis, if the spasm shuts off enough blood for a sufficiently long time, an actual lesion in the retina may result; this lesion is not reversible by reduction of the spasm, although it may ultimately heal by other processes.

This is illustrated by case 12 (and others). In case 12, the patient's central scotoma lasted about six weeks, when it disappeared. It was never affected by use of papaverine hydrochloride, although the shifting scotoma around and often coalescent with it was affected. The larger scotoma was always abolished, whereas the fixed, central scotoma was not, and the latter stood out alone in fields plotted after administration of the drug.

The hypothesis is that the fixed, central scotoma represented a fixed lesion in the retina, which presumably had resulted from a vasospasm either more complete or of longer duration than the spasms responsible for the reducible scotoma. The reducible scotoma is interpreted as a consequence of transient or incomplete spasm which permitted the passage of enough blood, promptly or swiftly enough, to preserve the life of the tissue, but which, nonetheless, impaired function; the dilation of the vessel by the drug permitted the temporary reestablishment of normal nutritional conditions and the disappearance of the reducible scotoma.

RELATION TO THE PATHOGENESIS OF MULTIPLE SCLEROSIS

The hypothesis that the lesions of multiple sclerosis result from vasospasm emerges naturally from these observations. This hypothesis refers not only to disturbances affecting vision but to all the disturbances and lesions in the central nervous system, as suggested by the observations on diplopia and on intention tremor.

The observations reported here suggest that many of the scotomas associated with multiple sclerosis arise from disturbances in the retina itself. Obviously, this explanation does not preclude the possibility that some scotomas may result from disturbances in other parts of the visual system. All reasoning which we have applied to the findings is intended

to apply with equal validity to any part of the nervous system, not merely to the retina, on the assumption that the vascular conditions are the same in the retina as in the rest of the central nervous system.

The first point arising in opposition to the hypothesis that vasospasm produces the neural lesions is that the spasms might be a result, and not a cause, of lesions in the nervous system. This possibility is remote. Multiple sclerosis characteristically affects myelinated fibers, and not unmyelinated fibers, such as supply the blood vessels. Secondly, the symptoms affected by the drugs are not like secondary, coincidental phenomena; they are typical symptoms of the disease itself—scotomas, reduction in visual acuity, diplopia and the intention tremor. These facts indicate that the observed phenomena are not secondary to the disease; nor are they coincidental.

The reports of Horton and his co-workers⁹ on the beneficial effects of injections of histamine diphosphate in cases of multiple sclerosis will, like claims for any other mode of therapy of this disease, require many years of substantiation before the treatment can be accepted as useful. This effect is quite a separate matter, however, from the transient benefit from histamine diphosphate experienced by some patients while the flush is present. We have observed several patients who could walk more steadily during a flush following the subcutaneous administration of 0.0005 to 0.001 Gm. of histamine diphosphate. These changes in gait were not measured, but merely observed. The observations must be taken with some reservation, since there may always have been a psychologic effect. One patient could see well enough to read only while experiencing the flush; this, however, may have resulted from an effect of histamine diphosphate on the ciliary body.

The hypothesis that the vasospasms cause the lesions in the nervous system is supported in general by a number of facts concerning multiple sclerosis.

A. The scattered, unsystematic distribution of the lesions. This factor, associated with the studies in which he noted thrombi in small vessels suggested a vascular origin to Putnam.¹⁰ It was the same factor and reasoning which led one of us (R. M. B.) to seek something in the blood itself which could affect myelin and to carry out experiments in which evidence of abnormal lipolytic activity was found. Confirmatory evidence was adduced by some observers, while others disputed

9. Horton, B. T.; Wagener, H. P.; Aita, J. A., and Woltman, H. W.: Treatment of Multiple Sclerosis by the Intravenous Administration of Histamine, *J. A. M. A.* **124**:800 (March 18) 1944.

10. Putnam, T. J.: Lesions of "Encephalomyelitis" and Multiple Sclerosis, *J. A. M. A.* **108**:1477 (May 1) 1937. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **38**:1 (July) 1937.

it. The evidence presented in this paper favors an origin from the vessels themselves, instead of from their contents, and this evidence appears more direct and cogent than the older evidences, which favored the blood.

B. The suddenness of onset of many attacks of multiple sclerosis. Massive attacks, producing serious incapacity, frequently appear suddenly, as is well known. Less well appreciated is the fact that single, slight symptoms also often occur suddenly; minor as these symptoms are from the standpoint of incapacity, they are nonetheless attacks of multiple sclerosis. These are very common, and the case records of one of us (R. M. B.), made long before these investigations began, contain many examples. We refer to new symptoms, or to sudden recrudescences of old ones which had improved, and not to the daily fluctuations which are common with all symptoms.

C. The brevity of duration of some symptoms. Close questioning of patients with multiple sclerosis often discloses sudden onsets of transient phenomena, which may last no longer than a few minutes. Examples, culled from the old records of one of us (R. M. B.) long antedating these studies, are given.

V. S.: March 15, 1937: The right leg appears to be weak at times, which makes the patient quite unsteady when she walks. This condition seems to come and go; she walks in this unsteady manner and then two hours later is able to walk in a practically normal manner.

Two or three days ago the patient woke up with a slight attack of double vision, which has also appeared and disappeared at different times of the day.

M. J.: Oct. 9, 1940: The patient's vision becomes blurred after eating and remains so about fifteen minutes.

Jan. 16, 1942: A peppery taste at the end of the tongue has occurred two or three times daily in the past three months; this seems to be worse in strong light or on the patient's attempting to read.

A. H.: Sept. 12, 1940: Three or four weeks ago, while carrying two heavy bags, the patient ran to make a train, and his right leg became "like a dead limb." It felt normal again after he had rested on the train. He had experienced this once before, after climbing a mountain.

H. B.: Aug. 4, 1937: There has been a recurrence of a pins and needles sensation in the tips of all the fingers of the left hand; this sensation occasionally travels up the front of the left hand, and sometimes up the arm to the neck.

N. G.: Feb. 17, 1938: After ten minutes of steady walking, the patient has a feeling of tingling in both thighs and in the buttocks, which lasts about five minutes.

J. F.: Jan. 4, 1936: A moving "dart" before the eyes, present for a long time, is sometimes one big spot and sometimes a "veil of spots."

H. A.; April 10, 1936: The patient experienced sudden weakness while pulling an object in a bending position; this lasted fifteen minutes.

In June or July 1932 he had had noted peculiar sensations in the upper teeth on the right side, especially when frightened or excited. This disappeared in about three weeks.

N. S.: Dec. 3, 1937: In October 1937, while in the subway, the patient had an attack of oscillating vision for about an hour.

E. N.: Aug. 5, 1937: The patient first noticed a momentary feeling of numbness and tingling in all the fingers and in both arms as far up as the elbows.

J. U.: July 10, 1942: The patient's vision became blurred after she had been swimming recently.

Sept. 25, 1943: The patient had an episode of double vision for about ten minutes two weeks ago.

The present series includes 7 cases in which sudden onsets of transient symptoms occurred in known circumstances: case A, in which sudden bright light or sudden emotional tension precipitated attacks of blindness in the left eye; case B, in which hot baths brought on "shimmering vision" and scotomas; cases 13 and 14, in which the act of eating, particularly the taking of a hot drink, caused spasms to appear, with increase in visual impairment (not confirmed objectively); case 20, in which the smoking of a cigaret accentuated the intention tremor; case G, in which an intention tremor was also increased with smoking, and case F, in which, according to the history, the patient experienced diminution of vision when under a hot hair dryer (we did not observe this ourselves). In addition, in case 2 and case C the most noticeable, or only, diplopia occurred on arising in the morning. In all but the last 2 cases the symptom disappeared when the precipitating condition changed. In case 2 the diplopia disappeared in two to three hours, and in case C it improved noticeably in a few hours.

In suddenness of onset and brevity of duration these symptoms have a clinical similarity to those in cases of syphilitic endarteritis with transient monoplegia and in occasional cases of cerebral arteriosclerosis with single or repeated attacks of hemiparesis or other consequences which finally become permanent. The similarity suggests that the pathogenesis of the lesions in the central nervous system may be the same—reduction in blood supply.

D. The occasional symptomatic improvement with cessation of smoking. Corroborative, if not supportive, evidence is found in the symptomatic improvement—though never complete relief—which occasional patients note when they stop smoking. This statement by patients is also included in a number of our case records long anteceding the present investigations. The statement coincides with the observations made in case 20 and case G. An autonomic effect on the phenomena of the disease is suggested. The situation (incomplete improvement) may be similar to that of the immediately reversible component of a symptom associated with a fixed component.

Putnam¹⁰ and his associates described thrombi in some of the venules adjacent to the plaque and formulated the hypothesis that the neural lesions may result from the thrombi. It may be that the Putnam hypothesis and the one now presented are closely related. The thrombi

could be secondary to stasis associated with prolonged, intense arteriolar spasm, or to intimal injury when the spasm involves venules. Wagener^{8e} suggested that in cases of hypertension thrombosis of retinal vessels may follow injury to the vessel wall as a result of spasm.

ATTACKS AND REMISSIONS

Experimental.—It is necessary to stress the time factor in the experiments with drugs. The transient improvement in function could not have been due to spontaneous remission, for it followed the administration of the drugs immediately and regularly.

"Spontaneous."—It is quite possible that the sudden attacks of scotoma which occurred in some cases were actual attacks of multiple sclerosis if our hypothesis is correct. Many of these attacks had known precipitating causes, it will be remembered.

It would seem possible that many people might have such slight attacks as these at various times of their lives, in which the process is actually that of multiple sclerosis but which are not repeated and which do not result in fixed lesions. Such attacks might never come to the attention of the family physician or the neurologist.

If the hypotheses outlined are correct, two possible types of "spontaneous" remission would appear to be possible in the regular course of multiple sclerosis. One type could result from disappearance of vasospasms which were responsible for disturbances of function without permanent injury to tissue. "Acute remissions" of this type, although transient, appear to have occurred in these experiments. As long as the conditions causing vasospasm persisted, the disturbances of function returned presumably—although this was not demonstrated—as soon as the effect of the drug wore off. Observations many months later in some cases, such as 11 and 12, showed normal retinal vessels and no scotomas or visual impairment.

The other type of remission could follow the healing of actual lesions in the central nervous system. Illustrative observations have been recorded earlier in the paper (i. e., the central scotoma in case 12).

REFLEX ORIGIN OF SOME ATTACKS

The precipitation of sudden attacks of symptoms by light, heat, eating or emotional tension indicates that some of the vessels may become constricted by reflex action. It may be assumed that such vessels must be sensitized in some way for this to occur; presumably, it would not happen to vessels which had not previously undergone constriction for other reasons. There is some evidence that when this occurs it may involve, or at least include, the same vessels repeatedly; in case A it was the left eye alone which was involved again and again, for several years. Yet later the right eye became included as well.

Eliciting of attacks by heat coincides with the report of Simons¹¹ on the rapid, untoward symptomatic effects of heat in many cases of multiple sclerosis. Exposure to the hot sun may rapidly increase all the symptoms in these cases.

FUTURE PROBLEMS

Additional research is now needed, first, into the cause of the spasms. This is entirely unknown. Allergy suggests itself, but only a few of the patients with spasm were known to have been afflicted with allergy in any form. In 1939 Baer and Sulzberger¹² tested for atopy a group of patients with multiple sclerosis at the Montefiore Hospital and a group under the observation of one of us (R.M.B.). The incidence of atopy was "little higher than that to be expected in any equivalent unselected group studied by the same methods." This does not mean that multiple sclerosis may not be influenced by allergy in a patient who has both conditions. Kennedy¹³ described cases in which the disease was clinically indistinguishable from multiple sclerosis and allergy appeared to play a potent role, and we have seen some cases as well. However, no correlation has yet been found between allergy and the vasospasms we have described.

Some observers believe that multiple sclerosis is a syndrome, representing more than one cause. This may be true, and vasospasms may prove to occur in only one group. Further study will be needed to elucidate this point.

Additional symptoms of multiple sclerosis should be studied according to the principles employed in this investigation. Such symptoms should be new, or should have a new component. The symptom should be recordable in some objective way. The observations should be made just before and just after the administration of vasodilating drugs.

THERAPY IN TERMS OF THE HYPOTHESIS

Therapeutic efforts have been commenced on the foundation of these observations. The hypothesis would call for continued vasodilatation of the vessels of the nervous system, as well as for the prevention of spasm. Both these measures should be in force for twenty-four hours a day. A drug-free interval of even a few minutes would suffice for an attack. We have no certain means of maintaining uninterrupted

11. Simons, D. J.: A Note on the Effect of Heat and of Cold upon Certain Symptoms in Multiple Sclerosis, *Bull. Neurol. Inst. New York* 6:385, 1937.

12. Baer, R. L., and Sulzberger, M. B.: Role of Allergy in Multiple Sclerosis, *Arch. Neurol. & Psychiat.* 42:837 (Nov.) 1939.

13. Kennedy, F.: Allergic Manifestations in the Nervous System, *New York State J. Med.* 36:469, 1936.

vasodilatation at present. A far better approach might be employed if the fundamental cause of the spasms could be ascertained.

In the meantime, we have used what resources were available. These include oral administration of papaverine hydrochloride, sometimes in doses as large as 0.045 Gm. every two hours when the patient is awake; aminophylline; belladonna in a dosage sufficient to cause and maintain visual blurring; syntropan, and histamine diphosphate, given according to the method of Horton and his co-workers. Histamine diphosphate has also been given subcutaneously in doses of 0.005 to 0.001 Gm., repeated every fifteen or twenty minutes for three or four doses, in such a way as to maintain a flush for sixty to ninety minutes. This mode of administration, which is simpler than the infusion, was first suggested by a junior member of the house staff of Mount Sinai Hospital, whose identity has been lost. Whisky or wine has also been administered in continuous small doses for several days and nights, in sufficient doses to maintain a feeling of being affected by alcohol. Recently we have employed benadryl and pyribenzamine hydrochloride.

No report can be made as yet on the effect of any of these therapeutic attempts except to say that several patients have regressed while taking benadryl or pyribenzamine. Possibly these drugs may be more helpful to other patients. We have gained only an impression that a combination of syntropan (up to 0.7 Gm. per day) and aminophylline in tolerance doses may be more effective than the other drugs. In cases of multiple sclerosis the spontaneous remissions interfere with the evaluation of treatment, and it is necessary to observe patients for a long time in order to satisfy whatever criteria we use for evaluation. Conclusions should be based not on how many patients improve, but on the incidence of regressions and of new symptoms over a long period.

The possibility of paradoxical reactions should be kept in mind in treating patients according to the hypotheses presented here. Such reactions were observed in case 11. The assumption must be made that fixed lesions in the vessel walls associated with a paradoxical reaction to drugs would be harmful to the patient and that perhaps vasoconstricting drugs should be substituted in such a case. We have seen at least 1 instance in which the patient gave the appearances of doing well on syntropan combined with aminophylline, then suddenly regressed and promptly improved again when administration of the drugs was terminated.

The frequency of precipitation of attack of increased impairment of function by such ordinary events of everyday life as eating and consuming hot drinks suggests that once the vessels are vulnerable to spasm almost anything may produce or accentuate it. One therapeutic indication may be the use of narcosis, with feeding by vein so as to produce as complete freedom from stimuli as possible.

SUMMARY

1. Observations on 18 patients with multiple sclerosis who showed constrictions of some of the retinal arterioles are reported. In 1 case, constriction was seen in a retinal venule. The observations are summarized as follows:

(a) The constrictions appeared (1) as isolated areas of narrowing in limited parts of arterioles; (2) in hourglass form, and (3) in segmented form (broken columns of blood were seen in the vessels, with white areas between them). In addition, alternating opening and closing of an arteriole were seen in 3 cases. In 1 instance constrictions kaleidoscopically appeared and disappeared in the whole arteriolar tree while the examination was proceeding. Pulsations of the whole arteriolar tree were seen occasionally.

(b) Scotomas were usually associated with the constrictions, and sometimes there was also reduction in visual acuity. The objective findings coincided with the patient's subjective complaints. Some patients complained of a shimmering of the object seen, which caused its outlines to be blurred.

(c) In most instances in which they were employed, fast-acting vasodilating drugs caused prompt, temporary reduction of the constrictions and of the size of the scotomas (sometimes to zero). In several instances there was an increase of visual acuity as well.

The drugs used were amyl nitrite, administered by inhalation, and papaverine hydrochloride, administered by vein.

(d) In 4 cases with early or transient diplopia, the degree of diplopia was reduced by the inhalation of amyl nitrite.

(e) The intention tremor in 2 cases was increased by the smoking of a cigaret. In 1 case, the intravenous injection of papaverine hydrochloride prevented this effect; the imbibing of liquor also prevented it and transiently abolished the basic intention tremor as well.

(f) Constrictions and scotomas were both found frequently to be multiple and to shift in position.

2. The constrictions are regarded as spasms.

3. The hypothesis is developed that the lesions throughout the central nervous system in multiple sclerosis are caused by diminution of the blood supply which results from the spasms.

4. Evidence is presented which suggests the existence of two types, or grades, of scotoma and of diplopia—one transient and affected by vasodilating drugs; the other fixed and unaffected by the drugs. The two types may merge and be revealed jointly in one symptom. When the transient part is reduced by the drugs, the fixed part remains.

The hypothesis is proposed that the fixed lesions result from a vasospasm either more complete or of longer duration than the vasospasm responsible for the reducible symptom. The reducible symptom is interpreted as a consequence of transient or incomplete spasm which permits the passage of sufficient blood, promptly or swiftly enough, to preserve the life of the tissue, but which, nonetheless, impairs function; the dilation of the vessel by the drug permits the temporary reestablishment of normal nutritional conditions and the disappearance of the reducible symptom.

5. Attention is called to the frequency of sudden, brief attacks of minor, as well as major, symptoms in multiple sclerosis. In this series, attacks of visual disturbance are recorded as precipitated by heat (hot baths, hot drinks, sitting under a hot air dryer), by eating, by emergence from the dark into strong light and by emotional disturbance. In 2 cases the smoking of a cigaret caused exaggeration of the intention tremor. This evidence suggests that some of the vessels (presumably previously "sensitized" in some way) may become constricted by reflex action.

6. It is pointed out that the transient improvements in function could not have been due to spontaneous remissions, for they followed administration of the drugs immediately and regularly.

It is quite possible that the sudden attacks of scotoma which occurred in some cases were actual attacks of multiple sclerosis. In many of these there were known precipitating causes.

It would seem possible that many people might have such slight attacks as these at various times of their lives, in which the process is actually that of multiple sclerosis but which are not repeated and which do not result in fixed lesions. Such attacks might never come to the attention of the family physician or the neurologist. If the hypotheses outlined are correct, two possible types of "spontaneous" remission would appear to be possible in the regular course of multiple sclerosis. One type could result from disappearance of vasospasms which were responsible for disturbances of function without permanent injury to tissue. "Acute remissions" of this type, although transient, appear to have occurred in these experiments. The other type could follow the healing of actual lesions in the central nervous system.

7. No satisfactory evidence is available to explain the vasospasms.

Dr. Harry Van Dyke, professor of pharmacology, Columbia University College of Physicians and Surgeons, contributed advice concerning the use of the drugs and rendered other assistance. Mr. John Sheldon prepared the figures.

706 West One Hundred and Sixty-Eighth Street.
1000 Park Avenue.

LATE EFFECTS OF INJURY TO THE BRAIN DUE TO SHELL FRAGMENTS AND GUNSHOT

Neurologic and Psychiatric Observations

JOHN A. AITA, M.D.*

OMAHA

THE PURPOSE of this paper is to present observations on the physical and psychologic status of men with penetrating injuries of the brain seen in the late period of recovery. How are these men several months after they were wounded and on their arrival at a general hospital in the United States? How well have they tolerated cerebral injury under modern surgical methods and control of infection? What continuing problems, symptoms and defects do they have at this stage?

Reports on the residual signs of craniocerebral injury often evidence little regard for underlying pathologic or physiologic changes or factors in selection of cases. It was demonstrated by Denny-Brown¹ and emphasized by Lynn and associates² that there is a difference in the intracranial alteration produced by trauma of the acceleration-deceleration type, crushing trauma and penetration of missiles. In the first type of trauma diffuse cerebral alteration results; in the other two, focal injury. I believe it is extremely rare that pure focal injury occurs. The laws of physics of penetrating missiles indicate a wide dispersion of energy when the brain is penetrated.³ The presence and duration of post-traumatic amnesia in cases such as I shall present likewise indicate diffuse cerebral alteration.¹

The observation of large numbers of cases of craniocerebral injury leads to an awareness of factors of selection. All survivors of severe head wounds are evacuated to a neurologic-neurosurgical center. In the case of the patient with a simple fracture or a minor scalp wound and only brief unconsciousness and amnesia, the story is different. He will

*Formerly Captain, Medical Corps, Army of the United States.

1. Denny-Brown, D.: Cerebral Concussion, *Physiol. Rev.* **25**:296-325 (April) 1945.

2. Lynn, J. G.; Levine, K. N., and Hewson, M. A.: Psychological Tests for the Clinical Evaluation of Late Diffuse Organic, Neurotic and Normal Reactions After Closed Head Injury, *A. Research Nerv. & Ment. Dis., Proc.* (1943) **24**:296-378, 1945.

3. Fulton, J. F., in discussion on Gurdjian, E. S., and Webster, J. E.: Experimental and Clinical Studies on the Mechanism of Head Injury, *A. Research Nerv. & Ment. Dis., Proc.* (1943) **24**:48-97, 1945.

not be evacuated unless he manifests continued complaint and disability sufficient to warrant release from duty and evacuation. Thus, there may be selection by means of continued complaint. I believe that this factor of selection operates also in reports of many civilian statistics and is often overlooked.

It is with these facts in mind that I present a series of 100 cases. In all instances, wounds were produced by flying, penetrating missiles under conditions of combat, and the dura and the brain were known to be wounded. For the most part, then, selection occurred only so far as the men were selected for army and front line combat duty. Otherwise, it can be assumed that the series studied is a representative cross section of survivors so wounded, for they all had to be evacuated.

MATERIAL

In a series of 320 consecutive admissions of men with head injuries to an army neurologic-neurosurgical center in the zone of the interior, there were 100 cases of open head injury with surgically proved penetration of the dura and injury of the brain due to shell fragments or gunshot. Most of the men arrived at the hospital within six months of their being wounded and remained three to nine months. All were personally examined and observed by me during their entire period of hospitalization.

DATA

Age.—Fifty-one patients were under 25 years of age; 45 were in the age group of 25 to 34 and 4 were 35 or older.

Time Between Injury and Admissions to Hospital.—Thirty-eight men arrived at this hospital less than three months after they were wounded; 40, from three to six months after injury; 18, from seven to twelve months after injury, and four over a year later. Causes of tardy appearance at this center included severe wounds prohibiting evacuation; wounds of parts other than the head, especially orthopedic injuries (which required primary attention), and previous treatment at other neurologic-neurosurgical centers.

Cause of Wound.—In 87 cases the wounds were produced by shell fragments, and in 13, by gunshot.

General Impression of Severity of Injury to Brain.—The final diagnosis set forth on each patient's record required an estimation of the severity of the injury to the brain. Any attempt to quantify injury to the human brain, even when the necropsy specimen is available, is admittedly subject to many criticisms. However, a crude clinical impression was reached in each case, and the designations of mild, moderate or severe injury to the brain were used. It was realized that no clearcut delineations were possible. Injury may be extensive in some portions of the brain and yet betray only mild alteration on clinical observation. Cerebral injury may be actually minor from the

pathologic standpoint but located in such a manner as to produce much observable motor, sensory or psychologic dysfunction. In the previously intellectually dull soldier or in the schizoid patient, the impression may erroneously be reached that profound psychologic alteration ascribable to cerebral damage has occurred. Psychoneurotic and psychoneurotic-like problems arising after head injury may likewise confuse the issue.

In arriving at the clinical estimate, commonly accepted criteria were used, such as the surgeon's data (presence of foreign bodies, degree of penetration, destruction of the brain and meninges, extent and locus of débridement, herniation, fungation and infection); duration of unconsciousness, delirium and amnesia; subsequent complaints and defects; neurologic signs; spinal fluid findings; psychologic performances; clinical course and degree of recovery to date: electroencephalographic disturbances; roentgenographic changes in the skull and, at times, pneumoencephalographic evidence, and knowledge of the patient's previous attainments, personality and background. The integration of these facts was used, rather than any single yardstick or mathematical formula.

1. In 9 cases the diagnosis was mild injury of the brain. The following case is illustrative of this group:

A private aged 20 was wounded five months prior to arriving at this hospital by fragments of a high explosive shell which struck the right preauricular region, penetrating the right temporal squamosa at the base of the skull, the right maxillary sinus and the right mandibular joint. He recalled being struck and became unconscious for an unknown period; he was then delirious and amnesic for three days. The surgeon's report indicated a laceration of the dura and a small shell fragment immediately beneath it. No further tract was observed. A small herniation followed initial débridement but cleared spontaneously. The only neurologic signs recorded indicated partial paralysis of the right third nerve, which likewise disappeared. Recovery was otherwise uneventful except for a great number of complaints and right maxillary sinusitis, which responded to puncture of the antrum. On arrival at this hospital, the patient complained of right-sided headaches, excessive nervousness and constipation. Social service investigation, psychologic testing and psychiatric study of the patient revealed serious pre-existing psychoneurotic difficulties. Intellectual loss due to damage to the brain could not be demonstrated. The electroencephalographic tracing was normal. Neurologic examination revealed only hypesthesia over the first two divisions of the right fifth cranial nerve.

2. In 61 cases the diagnosis was moderate injury to the brain. The following case is a common example of this group:

A 23 year old corporal was wounded by shell fragments low in the right occipitoparietal region five months prior to entry to the hospital. The laceration of the scalp was approximately 6 cm. long. A large defect in the skull, measuring approximately 8 cm. in length and 4 cm. in width, was the result of operation. Many fragments of bone were removed from a tract at least 2 cm. deep. The

patient did not recall being struck, was unconscious for several days and had no recollection of the ten days following the day on which he was wounded. Hernia cerebri with moderate infection developed but subsequently disappeared. He was bedridden one month. On arrival at this hospital, he complained of visual loss and awkwardness of the left arm and leg. A roentgenogram revealed a large defect in the skull with radiating fracture lines extending into the floor of the middle fossa. Neurologic examination revealed left homonymous hemianopsia; the left pupil was larger than the right; both pupils reacted poorly to light; there were slight hemiparesis and astereognosis on the left side and anosmia on the right. Careful psychologic investigation indicated intellectual defects, which, however, did not appear to be immediately disabling. The electroencephalographic tracing disclosed only a generalized distribution of borderline slow waves.

3. In 30 cases the patient was considered to have suffered severe injury to the brain. A typical example follows.

A 20 year old private was wounded by shell fragments six months prior to entry to this hospital. He was struck in the right occipital region, the missiles penetrating the left frontal region and producing a large tract with small foreign bodies throughout. Initial roentgenograms revealed that the largest foreign body would roll back and forth in the tract as his head was turned from side to side. He also incurred a compound, comminuted fracture of the radius of the right arm and severe lacerations of that arm. He did not recall being struck, was unconscious six days and remained delirious and amnesic for the ensuing six weeks. Signs of decerebrate rigidity were present during this time. Recovery was stormy. On arrival at this hospital he was bedridden and triplegic and demonstrated complete left homonymous hemianopsia and cortical sensory loss over the entire left side of his body. He confabulated somewhat, although he was correctly oriented. He was unstable emotionally and became enraged easily. His electroencephalographic tracing revealed a focus of very slow waves in the right occipital region. Social service investigation disclosed that in civilian life he had had average intelligence. One year after he was wounded samples of his intellectual performance indicated abilities in the mental age range below 13 years.

Other Details Concerning the Wounds.—Penetration deeper than 2 cm. into the brain tissue was ascertained in 60 cases from surgeons' notes and the presence of foreign bodies. Accompanying hematomas (subdural or intracerebral) were described in 10 cases. Evidence of infection complicating recovery was found in 26 instances. In 10 cases cerebral hernia was reported. In 2 cases there was full blown meningitis (eventually controlled by chemotherapy). Localized and superficial infection was the most common type of infection reported. In 2 cases there was definite evidence of extradural abscess. Osteomyelitis of the skull was a complication in 4 cases, in 3 of which several renewals of tantalum plates were required. The number of cases of infection after arrival at this hospital was small and diminished as the war progressed. It appeared as time went on that patients were evacuated less rapidly to the zone of the interior, for which reason more time and energy could be devoted to the clearing up of infections. In 15 cases infection was present on the patient's arrival here. In 4,

it was primarily chronic, localized osteomyelitis of the skull; in the remaining cases it consisted of chronic superficial infection in the scar site, involving the brain (locally) in 6 instances. Recurrent meningitis occurred in 1 case but was adequately controlled with chemotherapy.

Site of the Wound.—In 30 cases the frontal bone was primarily involved and in 30 others the occipital bone. In the rest of the cases the injury was classified loosely as parietal. In 16 cases the wound was located in the vertex and extended across the midline. In 3 cases the injury was classified as multiple, the wounds having been incurred at several cranial sites simultaneously.

Presence of Other Wounds.—In 37 cases wounds were incurred elsewhere than in the head. In 13 cases these wounds were of major proportion, with the following distribution: fracture of a large, long bone and multiple soft tissue wounds, 5 cases; fracture of more than one large, long bone, 2 cases; fracture of only one large, long bone, 2 cases; abdominal and visceral perforations, 3 cases; perforation of the chest with pneumohemothorax, 1 case. The presence of these wounds could not be shown to have any effect on recovery from the cerebral injury. There was no clinical reason to suspect fat or air embolism in these cases.

Recall.—Of 80 cases in which information on the point was obtainable, the patient recalled having been struck by the shell fragments or having received the gunshot wound in 50 (62 per cent). Of the remaining 30 (38 per cent), 10 (12 per cent) had a retrograde amnesia, in addition to amnesia for the injury. There was every indication that men who could not recall being struck were more severely wounded.

Duration of Unconsciousness.—From the records of 62 men an estimate of the state of consciousness following injury was possible. Of these 62 patients, 13 (21 per cent) apparently were not unconscious at any time. This was ascertained from the patient's statements, as well as from field medical records. Eleven (18 per cent) were unconscious less than fifteen minutes. Concerning the remainder, estimations became exceedingly difficult because the cessation of "unconsciousness" was vaguely defined. Maintenance of records under conditions of combat was of necessity difficult. Some patients evidently became unconscious repeatedly, so that a second or a third period of unconsciousness would have to be considered. Operative procedures, anesthesia and preoperative and postoperative sedation often confused these estimations. Of the men rendered unconscious, it was ascertained that approximately one-third were not immediately rendered so.

Duration of Post-Traumatic Amnesia.—Discussion of the anamnesis with the patient and a careful review of his records provided a reason-

able estimate of the duration of amnesia following his wound. My colleagues and I endeavored to adhere to strict criteria in defining amnesia.⁴ The subjective experiences of being "dazed," "in a fog" or "forgetful" which the patient recalled at the time of treatment were not considered significant. Of 73 cases in which data were obtained, there was a history of post-traumatic amnesia of less than twenty-four hours' duration or none at all in 18 (25 per cent). In 16 per cent it lasted one to three days; in 29 per cent, four to seven days; in 8 per cent, eight to fourteen days; in 8 per cent, fifteen to twenty-one days, and in 14 per cent, over twenty-one days. Prolonged amnesia was found to be correlated with the presence of definite neurologic signs, amnesia for the wound incident, "organic facies" and intellectual loss. It cannot be overlooked that operative procedures, anesthesia, sedation, infection and dehydration likewise contributed to the production of prolonged amnesia. However, the exact role that these factors played could not be ascertained in this group of men, who had been treated under combat conditions.

Chief Complaint on Entry.—Headache was the commonest complaint, appearing in 39 cases. However, in only 9 cases was it severe enough to cause the patient routinely to seek rest or medication. In 15 instances distress was primarily at the site of the wound, and in 18 others it was in that general quadrant. In 2 cases distress was localized to the wounded side of the head, and in 4 others, to the opposite side. In 6 cases sharp, jabbing pains in the scalp were described. In 18 cases continued attenuation of distress was admitted. A survey of precipitating and aggravating factors (by means of a standard questionnaire concerning one hundred conditions) revealed that during hospitalization headaches were most commonly precipitated and aggravated by visual strain and emotional reactions. Jarring, exertion, train rides and positions in which the head is low were also incriminated, but less prominently.

In 33 cases the patient complained of visual disturbances. Destruction of the geniculocalcarine pathways or the calcarine cortex was at fault in 26 cases. In 6 instances one eye was damaged (in addition to destruction of the geniculocalcarine pathway in 2 cases, so that the patient had only partial vision in the remaining eye). In 3 other cases visual loss was due primarily to destruction of the optic nerve fibers in or anterior to the chiasm.

In 52 cases motor disability in one or more extremities was complained of. In 18 instances this amounted to complete hemiplegia; in 7 others, to triplegia or paraplegia, due to midline involvement of the paracentral lobule.

4. Psychological Terms Used in Cases of Head Injury, Medical Research Council, Great Britain, Brit. M. J. 1:525 (April 5) 1941. Russell, W. R.: Accidental Head Injuries: Prognosis in Service Patients, Lancet 1:7-10 (Jan. 2) 1943.

Language dyspraxia and dysgnosia ("aphasias") were present in 20 cases. The commonest overt disabilities concerned expression in speech and writing.

Dizziness (not true vertigo) was a complaint in 9 cases; tinnitus, in 8 cases, and deafness, in 9 cases. Anxiety symptoms, such as tension, hyperhidrosis, combat dreams, insomnia, nervous trembling and palpitation, were complained of in 11 cases, but in only 4 cases could they be considered moderately severe. In 4 cases frequently recurrent convulsive episodes comprised an important complaint. Diplopia was present in 5 cases and anosmia in 6 cases. In 1 case there was complete paralysis of the facial nerve (peripheral type). In 6 cases intellectual defects were complained of, although in other cases of such defects the patient appeared to lack insight thereof on arrival. In 8 cases there was no complaint whatever.

Gross Estimation of Disability on Arrival.—Disability was graded on the over-all impression of mental and physical incapacity. The patient who was bedridden or wheelchair-ridden, requiring assistance to eat, dress and attend to his toilet, was graded as severely disabled. So was the occasional man with so great an intellectual loss that his performance was now considered at or below the borderline of mental deficiency. Thirty of the 100 patients appeared to merit classification as severely disabled.

A moderately disabled soldier could get around on crutches or with a cane and had at least a dull normal retention of general intellectual assets. Twenty-eight men were regarded as belonging to this category.

The typical mildly disabled man had paresis of one or two limbs, hemianopsia or mild "aphasia." Twenty-four men were in this category.

The patient with only subjective disability presented no objective signs or deficits (other than defects of the skull). There were 14 such patients. Four men exhibited no complaints, objective signs or disability (other than defects of the skull).

Defects of the Skull.—On arrival at this hospital, all the men had defects of the skull. Many, if not most, of these defects were of the magnitude encountered as a result of débridement. It appeared that the size of the defect had more to do with the surgeon's discretion and habits than with the severity of the injury. Estimation in terms of square centimeters of area revealed defects of 2 to 10 sq. cm. in 46 cases, of 11 to 20 sq. cm. in 29 cases and of greater than 20 sq. cm. in 25 cases. In addition to these defects, radiating fracture lines were demonstrated in 32 cases. The presence of fracture lines radiating from these defects correlated significantly with indicators of severe damage to the brain.

Other Complicating Factors in Convalescence.—In 12 cases convalescence was complicated by a prisoner of war status, acute appendicitis,

malaria, severe frostbite, trench foot, postoperative pulmonary infarcts or abscess, hypertension, acute hepatitis due to infection and intestinal parasites. None of these complications, however, could be shown to be deleterious in the recovery of the men from their cerebral injury.

Neurologic Findings.—The cases were divided into three groups on the basis of the neurologic findings: (1) no neurologic changes, in 9 cases; (2) minimal, scattered or nonlocalizing signs, in 20 cases, and (3) definite localizing neurologic signs, in 71 cases. In 58 cases of the last group the signs were of "motor" type (indicating plegia, paresis or manual dyspraxia). In 2 cases the disability was paraplegic, and in 5 it was triplegic. In 6 other cases, however, disability consisted in minimal paresis. In 26 cases lesions were demonstrated in the geniculocalcarine pathway or the calcarine cortex which resulted in defects in the visual fields. Residual evidences of language dyspraxia and dysgnosia ("aphasias") were present in at least 20 cases. From the records available, such disturbances had existed previously in at least 13 additional cases but were no longer detectable by clinical and psychologic tests after the patient's arrival at this hospital. Of the 20 cases with residual signs of dyspraxia and dysgnosia on arrival here, the disturbances were of relatively minor character in 9. In only 2 of the remaining 11 cases could the defects be considered severe, and in but 4 cases was strenuous reeducation for "aphasia" required. In the remaining 7 cases the aphasia cleared up remarkably with general intellectual stimulation.⁵ It is recalled here that in 48 cases of this series wounds had been received in the dominant hemisphere.

Astereognosis (usually associated with plegia or paresis) was found in 38 cases. Signs referable to the cerebellar tract were present in 5 cases (in 3 of which they were ascribable to direct involvement of the cerebellum). Clinical evidence of contrecoup injury could be established presumptively in only 5 cases—in 3 by neurologic signs, in 1 by the electroencephalographic tracing and in 1 by ventricular distortion in the pneumoencephalogram.

The cranial nerves were partially or completely involved as follows: olfactory nerve, 10 cases; third cranial nerve (including its nuclei), 9 cases; fourth and sixth cranial nerves, 1 case each; fifth cranial nerve, 4 cases; seventh cranial nerve, 1 case of peripheral and 14 cases of central lesion; eighth cranial nerve, 4 cases (excluding cases of deafness due to other causes, including blast injury), and twelfth cranial nerve (paresis), 7 cases. Anisocoria was found in 18 cases; in 8 cases the larger pupil was on the same side as the site of injury.

Diabetes insipidus, from damage to the pituitary-hypothalamic complex was present in 1 case.

5. Aita, J. A.: Men with Brain Damage, *Am. J. Psychiat.* **103**:205-213 (Sept.) 1946.

In 29 cases the facies was characteristic of organic lesions. It consisted of a dull, washed-out, poorly expressive facial display. Expressions were slow to appear and disappear; they were listless, erratic, childlike, occasionally parkinsonian (masked, staring or immobile; 4 cases) or reminiscent of hepatolenticular degeneration (Wilson's disease) (fatuous, vacant facies, punctuated with sudden mechanical changes of expression, often stereotyped, such as a spastic grin; 3 cases). These findings were found to correlate significantly with severe cerebral injury and disability, deep penetration of the foreign body and prolonged delirium and amnesia, especially if the patient was not of prior dull normal intelligence.

Sensation of electric shock on flexion of the neck was present in 4 cases. This symptom is taken as an indication of concomitant injury to the spinal cord.⁶

Convulsive Seizures.—These had occurred at least once since the day of injury in 25 cases. In but 1 case was there uncertainty as to the nature of the disturbance, and in this instance the clinical picture of syncope (vasomotor?) was deemed a more likely diagnosis. In 8 cases convulsive seizures appeared within five months of the wound. In the remaining 17 cases seizures started later. Most of the men had only one to four seizures, at intervals of one to three months, which were easily controlled by medication. In 4 cases, however, seizures were more frequent and decidedly a major complaint, not easily managed by medication alone. In only 6 cases were jacksonian characteristics demonstrated.

Personality Change.—It was my repeated impression that the patient's present reactions and "personality" were not due to intracranial alteration alone. Personality phenomena which followed injury arose from both the personality of the wounded man and his now altered brain. Specific cases may serve as illustrations.

CASE 1.—Palpitation, morning vomiting and apprehension during convalescence. A study of the previous personality revealed that a pronounced sense of insecurity had been a lifelong trait, with enuresis up to the age of 15, nail biting and frequent nightmares prior to army service.

CASE 2.—Difficulty in rehabilitation despite average intelligence. When confronted with his irresponsible attitude toward rehabilitation, the patient complained of inability to decide what he would like to do. He frequently shirked classes and expressed multiple complaints and excuses. Social service investigation revealed

6. Allen, I. M.: Immediate and Remote Effects of Minor Lesions of the Cervical Portion of the Spinal Cord Following Head Injury, *Australian & New Zealand J. Surg.* 10:157-172 (Oct.) 1940. Walshe, F. M. R.: Commonly Unrecognized Type of Injury to the Cervical Spine and Spinal Cord in Association with Head Injuries, *Lancet* 2:173-175 (Aug. 5) 1944. Bender, M. B., and Furlow, L. T.: Sensations of Electric Shock on Flexion of Neck as a Sign of Head Injury, *J. Neurosurg.* 3:212-217 (May) 1946.

that the patient had been reared in meager socioeconomic circumstances and a turbulent family setting. He left home while quite young, did not get along with any member of his family and held no job longer than four weeks.

CASE 3.—Pronounced apathy and listlessness despite good intelligence ratings. The patient was constantly listless, uninterested and mildly depressed. He preferred to complain about his various disabilities, including complete paralysis of the right seventh cranial nerve. If left alone, he would sit, occasionally reading or listening to the radio. Discussion with his family revealed that he had always been apathetic, that he had to be "pushed" and could not decide (in the four years following graduation from high school) what he wanted to do. Sibling competition had left him drably passive and dependent.

CASE 4.—Lack of interest in rehabilitation. The patient, vociferous, enthusiastic and good natured, was found to be uninterested in any attempt to rehabilitate himself physically or psychologically. Discussion with his family revealed that he had been constantly unemployed in the interval between leaving school and entering the Army (a five year period), and he had always talked about getting a job but never had one. He had always been known for "tall tales," frequently telling people that he signed a contract to play for a famous national baseball team, when actually he was playing only local semiprofessional baseball. His occasional amusing confabulations during hospitalization were said by his family to be little different from those he habitually produced in civilian life.

CASE 5.—General irresponsibility, gambling, squandering and nomadism. A follow-up of the patient, who had a severe injury to the right frontal lobe, revealed that he was not working and that he was living a nomadic existence, gambled freely and was involved in minor illegal activities. Investigation of his background revealed that he had been reared by an aged aunt and uncle, toward whom he rebelled early in life, and that his present existence was but an exaggeration of the way he had lived prior to military service.

CASE 6.—Suspected personality changes due to frontal lobe deficit. The patient was noted for his excessive jocularity, irresponsibility, alertness and facetiousness. He amused every one with excellent repartee. At first it was readily assumed that he was suffering from a frontal lobe deficit. However, even after several furloughs home his family could see but little change from the personality they always had known.

In addition, several patients with schizoid reactions (1, to be described, had an actual psychotic episode) were found by social service investigation to have always had these outstanding trends.

Red Cross social service research, psychologic tests (the Wechsler-Bellevue scale,⁷ the Rorschach test⁸ and the Minnesota Multiphasic

7. Wechsler, D.: *The Measurement of Adult Intelligence*, ed. 3, Baltimore, Williams & Wilkins Company, 1944, p. 258.

8. (a) Armitage, S. G., and Reitan, R. M.: *A Critical Evaluation of Certain Psychological Measures, Including a Proposed Screening Test for Determination and Evaluation of Brain Injury*, to be published. (b) Klopfer, B., and Kelley, D. M.: *The Rorschach Technique*, New York, World Book Company, 1942. (c) Aita, J. A.; Reitan, R. M., and Ruth, J. M.: *Rorschach's Test as a Diagnostic Aid in Brain Injury*, *Am. J. Psychiat.*, to be published.

Personality Inventory⁹), psychiatric interviews and long term acquaintance with the patients during recovery and rehabilitation indicated changes in personality in 53 cases. Associated with severe cerebral injury and intellectual loss was the personality picture of the passive, listless, dull, apathetic soldier (10 cases). Euphoria, irresponsibility and poor judgment were outstanding in 6 other cases, although associated with direct wounds of the frontal lobe in only 3 cases. Except for certain intellectual deficits, few personality changes could be blamed primarily on cerebral damage, and many were ordinary, run-of-the-mill reactions of men who had experienced the army, combat and wounds. Of course, the patients with previous outstanding personality liabilities were in no way improved with cerebral injury and its experience. During hospitalization the incidence of psychoneurotic reactions was low, there being only 4 men who demonstrated a severe anxiety state (due for the most part to combat experiences). One other patient had complete flaccid paralysis of an upper extremity, which responded well to hypnosis. Three severely wounded men were noted for reactive irritability and temper outbursts, but they manifested a great drive for rehabilitation. In only 2 patients did a reactive depression appear (due primarily to incapacity), and in both the response to psychotherapy was good. Another soldier exhibited a schizophrenic-like psychosis after the covering of a defect in the skull with a tantalum plate. (There was no infection; the patient was well oriented, and of superior intelligence; he was involved in aloof, paranoid preoccupations and demonstrated inappropriate, facetious affect.) This condition disappeared in a few weeks except for residual schizoid signs. Four men became very dependent on hospital care and increasingly insecure about discharge. They devised numerous minor excuses and complaints to forestall their release. Only 1 patient was suspected of malingering (with the goal of receiving more compensation). Disciplinary problems were rare in this group of men, with many months of hospitalization. Only 1 man of the group was absent without leave; 1 became intoxicated frequently, and 1 was caught in naïve, readily discovered stealing. This record was in sharp contrast to that of the disciplinary problems repeatedly arising in other wards in this hospital where wounded men were undergoing treatment.

In only 25 cases did the men admit dreaming two to four times a week. Combat experiences were relived occasionally in 9 cases and frequently in 3 cases. One did not get the impression that these men had a great deal of nervousness due to combat experiences. Reasons for this scarcity of neurotic symptoms may be many. These patients

9. Hathaway, S. R., and McKinley, J. C.: *The Minnesota Multiphasic Personality Inventory*, Minneapolis, University of Minnesota Press, 1943, p. 16.

were an unselected group of wounded men, representing a cross section of all soldiers who fulfilled requirements for combat duty. It may be significant, also, that since they were wounded and were cared for as wounded men there was no biologic need to react with other symptoms. Their medical disposition was settled. Our laboratory aids, such as the Rorschach test and the Minnesota Multiphasic Personality Inventory, revealed significant neurotic responses in only one third of these men. (Indications of anxiety, depression and hypochondriasis were common in this group.)

The problems concerning most of these men were practical and concrete. What work could they do? What education could be sought? What pension would be obtained? Would the pension be decreased if they rehabilitated themselves and returned to work? What would be the ultimate effects of the wound? Would seizures develop? Would insanity, blood clots, hemorrhages, paralysis or cerebral tumor occur later? Would pneumoencephalographic studies or further neurosurgical procedures be necessary?

In a few instances, marital difficulties and family illnesses presented problems. Several men expressed much concern that they would be a burden on an already crowded home when they returned.

Estimation of Prior Intelligence.—On the basis of previous educational attainments, work records, social responsibilities, earnings, military skills and clues furnished by the present psychologic tests and by persons acquainted with him, each man was categorized according to his most likely prior intelligence level. Twenty-four men were rated as having superior intelligence (mental age estimated as over 18 years); 54 were considered of average intelligence (including high average and dull average ranges), and 22 of borderline defective intelligence (mental age under 12 years). Theoretically, the army sent no morons into combat.

Intellectual Losses.—It is reasonable to theorize that almost every patient included here lost some intellectual assets by his wound. In the more severely injured, deficits were evident to even the untrained observer. Yet among the men who suffered minor and probable discrete or superficial cortical damage, no intellectual losses could be diagnosed.

How could these deficits be estimated? We have found the following investigations helpful:

1. Psychologic study with the Rorschach test, the Wechsler-Bellevue test and methods suggested by Goldstein¹⁰ and others.¹¹ These tests

10. Goldstein, K.: *After Effects of Brain Injuries in War*, New York, Grune & Stratton, Inc., 1942.

11. Armitage and Reitan.^{8a} Aita and others.^{8c}

give clues as to prior and present performances, as well as to specific types of deficit often seen among persons with injury to the brain.

2. Social service investigation regarding the previous personality, educational attainments, social responsibilities, earnings, work record and changes now apparent to persons who had been closely acquainted with the patient for many years.

3. Clinical interviews with the patient; examination of his stream of thought, thinking difficulties and judgment.

4. Observation of the patient while on an active rehabilitation program by persons skilled in detecting intellectual difficulties.⁵

Allowance was always made for physical incapacities (such as deafness, aphasia, hemianopsia or hemiplegia) which might hinder performance on the more psychologic aspects of testing.

As physicians, we were concerned with one practical question concerning disability. Had this man's loss of intellectual assets been sufficient that it should be included in the official diagnosis, which would ultimately entitle him to veterans' compensation on the basis of post-traumatic encephalopathy, manifested by loss of intellectual assets?

In only 37 cases were deficits sufficiently impressive to require such a label. In 18 cases these deficits were striking. Clinical determination indicated that 14 men with previously superior intelligence had now slipped into the average range. Eleven men with previous average intelligence were now of borderline defective to defective intelligence. Twelve men with previously borderline defective intelligence were believed to have lost further assets (although this was the most difficult group to evaluate). On the basis of severe intellectual defects, custodial care was considered for 5 patients. Such care was actually found necessary for only 1 patient; the other 4 had excellent home settings and understanding families.

Severe intellectual losses were found in 8 of the 30 men with occipital wounds, whereas only 2 of the 30 men with frontal wounds demonstrated such severe deficits. (Posterior injuries often result in additional contrecoup contusion of the frontal lobes.¹²)

More interesting were the specific intellectual deficits demonstrated. The intellectual assets of men with these injuries are not devastated en masse, to reduce them to a more or less "feeble-minded" level.¹³

12. Courville, C. B.: Contre-Coup Mechanism of Craniocerebral Injuries, *Arch. Surg.* **45**:40-53 (July) 1942.

13. Goldstein, K.: The Significance of Mental Disturbance in Rehabilitation of Soldiers with Brain Injury, *Tr. Am. Neurol. A.* **70**:22-24, 1944; The Problem of Cerebral Localization from a Clinical Point of View, in Halloran, R. D., and Yakovlev, P. I.: *Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry*, Waltham, Mass., Metropolitan State Hospital, 1942, p. 530, lecture 14. Footnote 10.

Rather, deterioration, whether great or slight, is uneven and selects certain intellectual assets, permitting others to remain remarkably preserved. The deficits and distress of these men cannot be understood unless these spotty defects are known.

Patient, family, employer and physician alike may be unaware of specific intellectual deficits because retention of other assets permits covering up or substitution. These men with intellectual losses frequently retain previously accumulated factual data, the common information of everyday adult life, vocabulary and verbal abilities, old memories, habits and concepts previously learned and the ability to handle readily meaningful or concrete concepts. They can often manage the problems immediately at hand, especially if these can be dealt with unreflectively. They frequently use trial and error methods successfully, without detection by persons untrained in recognizing their deficits. In addition to demonstrating these intellectual retentions and adjustments, performances reveal dogged perseverance and perfectionism, strict adherence to directions and retention of social amenities—all of which may be very disarming.

Psychologic tests¹⁴ of intellectual components revealed loss of ability to analyze and synthesize. These patients were unable to change their method of attack on problems or to shift attitudes or concepts. Memory defects were manifest for recent occurrences. The men lacked anticipation, organization and planning ability. They were unable to deal comprehensively with variables, more than one aspect of a problem or dual relationships. It was difficult for them to handle new problems, especially those not depending on old information and habits. Attention and concentration were impaired, being especially sensitive to anxiety. Their thinking often showed evidences of helpless repetitiousness and stereotypy, or actual perseveration. They tried doggedly, often recognizing some inadequacy, but were helpless to change their attack.

Electroencephalographic Tracings.—Records were declared normal in only 10 cases. In 52 cases they were borderline normal¹⁴ including records of generalized moderately slow and moderately fast activity. In 38 cases the records were classified as showing abnormal, very slow, very fast or focal (or spiking) activity. In 23 cases records of focal activity were obtained. Asymmetry of amplitude was present in the records of 75 men. The majority of electroencephalographic abnormalities were found in the records of patients most recently wounded.

14. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: *Electroencephalographic Classification*, Arch. Neurol. & Psychiat. 50:111-128 (Aug.) 1943. Gibbs, F. A., and Gibbs, E. L.: *Atlas of Electroencephalography*, Cambridge, Mass., Lew A. Cummings Company, 1941. *Electroencephalography: Operative Technique and Interpretation*, United States War Department Technical Bulletin (TB Med. 74) Washington, D. C., Government Printing Office, July 27, 1944.

Besides the initial records described in the preceding paragraph, three serial records were obtained in 62 cases over an average period of six months. Although in 54 cases tantalum plates were inserted at one time during the study we could not prove that this procedure affected the electroencephalographic tracings subsequently obtained. In 18 cases (30 per cent) definite improvement occurred in the record, and in 8 cases (13 per cent) a greater degree of abnormality appeared. Asymmetry of amplitude appeared later in one third of the records which did not demonstrate it initially. It remained in one half of the records in which it appeared initially. These facts could not be correlated with available clinical data.

Course of Physical Disability.—On arrival at this hospital, 9 men were bed patients. On discharge, 5 of these were actively ambulatory, 3 of whom required a cane. The remaining 4 were triplegic with persisting paraplegia requiring dependence on wheelchairs. On arrival here, 14 others entered as wheelchair patients. All these men became actively ambulatory before their discharge, 5 of whom continued to require a cane. Fourteen men (out of this total of 23) had a useless upper extremity on discharge.

Continued disability could not be accounted for merely on the basis of the severity and location of the injury as such. Neither could it be fully understood by mere knowledge of the presence of convulsions or hemiplegia. Bare neuropathologic or neurophysiologic summaries of what the injury had produced left much to be desired. Only when the patient concerned was studied could the entire picture of disability be comprehended.

Prognosis.—On the patient's discharge from this hospital, each case record bore a prognosis. This was ascertained primarily from the standpoint of practical employability. It did not consider unpredictable seizures. In 7 instances the prognosis was "poor," predicting a lifetime of total incapacity—wheelchair existence, mental impairment and inability to care for more than simple needs.

In 30 cases the prognosis on discharge was "fair." In these cases there was physical and/or mental impairment, but part time or simple occupational adjustment warranted anticipation.

In 46 cases the prognosis was rated as "good." These men suffered only minor impairments and/or subjective symptoms. It was anticipated that they could not attain previous levels of work efficiency but they should be able to work full time.

In 17 cases the prognosis was "excellent" because the men had inconsequential impairment (barring the future development of convulsions), and tentatively they were considered "as good as before."

Rehabilitation in the Hospital.—This has been described in detail elsewhere.⁵ It included a carefully integrated and individualized program designed to assist each man to relearn and to compensate for and circumvent his defects.

Dispositions.—Eighty-three men were given medical discharges directly from this hospital. Six others were transferred first to a convalescent center and subsequently given medical discharges. Seven men were sent to other specialty centers (ophthalmology or otology or plastic surgery). Only 4 patients were transferred directly to a veterans' hospital. With 3 of these men this transfer was necessary primarily because of severe physical handicaps; with the other, because of intellectual impairment, euphoria, irresponsibility and insufficient assets and understanding at home to assist in continued rehabilitation. It appeared evident to all medical officers who saw these patients at disposition boards that the men with a prognosis of "excellent" could have been returned to duty, and many of those rated as "good" could likewise have continued to serve in a limited capacity.

SUMMMARY

The recent war has brought numbers of young, healthy men with severe alteration of intracranial structures, who, for the first time in history, will live and somehow adjust because modern neurosurgical skill and control of infection have allowed them to. These young men will be with us for many years, and their problems of distress, deficit, disability and pension will be encountered repeatedly not only by the specialist but by the general practitioner as well.

I have described observations in a representative cross section of men with penetrating injuries of the brain during the late phase of recovery. Unlike men with the post-traumatic syndrome (following closed head injury or concussion), who were usually evacuated only on the basis of continued complaints, all these men were evacuated because of the location and nature of their wounds. Hence, we saw a cross section of all soldiers so wounded.

Findings were presented in detail, and from these the general plan of study and evaluation of each patient was evident. On his admission, the immediate problem concerned what had happened to him. He and his previous medical records were searched for clues. This information, together with neurologic examination and laboratory technics, permitted a diagnosis of the alterations which were present, their location, severity and course to date. Neurosurgical considerations were constantly required.

The patient who had the injury and consequent disabilities was scrutinized. Who was he before this injury? Personality characteristics, family setting, life experiences, attainments and anxieties comprised

part of the biologic material now altered. Combat, the wound, long hospitalization, treatment and convalescence, family and the future presented a constant stream of problems and anxieties. What had he left with which to continue life? His brain was altered, and he must go on variously, with motor defects, sensory distortions, convulsive seizures, loss of intellectual assets, headaches, dizziness or emotional instability. His was a struggle for adjustment to these confusing handicaps.

At the stage of recovery described, he had not encountered or experienced fully the range of complexity of his defects.

607 Medical Arts Building.

PSYCHOPHARMACOLOGIC STUDY OF SCHIZOPHRENIA AND DEPRESSIONS

III. Lactic and Pyruvic Acid Content of the Blood Before and After Administration of Sodium Amytal

R. M. FEATHERSTONE, Ph.D.

H. R. CARTER, B.A.

AND

J. S. GOTTLIEB, M.D.

IOWA CITY

IT HAS been reported ¹ that patients with schizophrenia or depression differ from each other in their clinical and psychologic responses to the intravenous administration of subnarcotic doses of sodium amytal followed by amphetamine sulfate N. N. R. One such prominent difference is in the development of tolerance to these drugs in terms of the type and duration of the psychologic response, which developed rapidly in patients with schizophrenia but more slowly in patients with depression.

Since barbiturates inhibit, in vitro, the oxidation of *d*-glucose, lactate and pyruvate in brain tissue,² may not the explanation of the differences in the responses of these two groups of patients to sodium amytal lie in differences of oxidation of carbohydrate? Looney³ reported that there is a relatively greater accumulation of unoxidized lactic acid in the blood of schizophrenic patients than in the blood of normal subjects as a response to graded exercise. He and Childs,⁴ moreover,

From the Iowa State Psychopathic Hospital and the Departments of Pharmacology (Dr. Featherstone and Mr. Carter) and Psychiatry (Dr. Gottlieb), State University of Iowa College of Medicine.

1. Gottlieb, J. S., and Coburn, F. E.: Psychopharmacologic Study of Schizophrenia and Depressions: I. Intravenous Administration of Sodium Amytal and Amphetamine Sulfate Separately and in Various Combinations, *Arch. Neurol. & Psychiat.* **51**:260 (March) 1944. Gottlieb, J. S.; Krouse, H., and Freidinger, A. W.: Psychopharmacologic Study of Schizophrenia and Depressions: II. Comparison of Tolerance to Sodium Amytal and Amphetamine Sulfate, *ibid.* **54**:372 (Nov.-Dec.) 1945.

2. Quastel, J. H.: Respiration in the Central Nervous System, *Physiol. Rev.* **19**:135 (April) 1939.

3. Looney, J. M.: Changes in Lactic Acid, pH , and Gases Produced in the Blood of Normal and Schizophrenic Subjects by Exercise, *Am. J. M. Sc.* **198**:57 (July) 1939.

4. Looney, J. M., and Childs, H. M.: The Lactic Acid and Glutathione Content of the Blood of Schizophrenic Patients, *J. Clin. Investigation* **13**:963 (Nov.) 1934.

indicated that there is an inverse relation between the amount of lactic acid in the blood and that of glutathione, a substance which is, or acts as, a coenzyme, in schizophrenic patients but not in normal controls. Stotz and Bessey,⁵ however, reported that the lactate: pyruvate ratio for patients with depression and schizophrenia did not differ significantly from that of normal subjects.

More recently, in general metabolic studies greater emphasis has been placed on pyruvate metabolism both in isolated tissues and in the intact organism. Stotz and Bessey⁵ and Friedemann and Haugen⁶ have advocated the use of the blood lactate: pyruvate ratio to distinguish true abnormalities of pyruvate metabolism from difficultly controlled fluctuations furthered by such factors as anoxia, exercise and food consumption.

The present study, therefore, was designed to answer the questions: Does the lactic or the pyruvic acid content of venous blood or their ratio differ among groups of patients with depression or schizophrenia and of normal subjects? Does the intravenous administration of sodium amytal produce differences in either lactic or pyruvic acid or their ratio in these three clinical groups?

METHOD

Determinations of the lactic and pyruvic acid contents of venous blood were obtained on 15 patients with depression, 12 patients with schizophrenia and 12 normal controls. Both before and one-half hour after the standard intravenous administration of 250 mg. of sodium amytal followed by 20 mg. of amphetamine sulfate N. N. R.,⁷ determinations of the amounts of lactic and pyruvic acids were obtained on 9 patients with depression, 8 patients with schizophrenia and 3 normal subjects. All patients and control subjects were in a basal state: complete rest in bed and no food for the preceding twelve hours. For each determination a sample of 5 cc. of venous blood was collected in a chilled 10 cc. syringe and was propelled through the needle into 5 volumes of cold 10 per cent trichloroacetic acid within forty-five seconds of the time of the withdrawal of the first cubic centimeter. The method of Friedemann and Haugen⁶ was used for the quantitative determination of pyruvic acid and that of Barker and Summerson⁸ for lactic acid. All determinations were made in duplicate and within three hours after the second withdrawal of the blood.

5. Stotz, E., and Bessey, O. A.: The Blood Lactate-Pyruvate Relation and Its Use in Experimental Thiamine Deficiency in Pigeons, *J. Biol. Chem.* **143**:625 (May) 1942.

6. Friedemann, T. E., and Haugen, G. E.: Pyruvic Acid: I. Collection of Blood for the Determination of Pyruvic and Lactic Acid, *J. Biol. Chem.* **144**:67 (June) 1942; II. The Determination of Keto Acids in Blood and Urine, *ibid.* **147**:415 (Feb.) 1943.

7. Amphetamine sulfate prepared for intravenous administration was supplied by the Smith, Kline & French Laboratories, Philadelphia.

8. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, *J. Biol. Chem.* **138**:535 (April) 1941.

RESULTS

The results of the analyses of the blood for lactic and pyruvic acids and their ratios, before and after the intravenous administration of sodium amytal, are shown in the accompanying table.

The lactic: pyruvic ratios for the groups of patients and for the normal controls before sodium amytal was given were compared for significance by the use of Fischer's t^9 : depressed versus schizophrenic patients, $t = 0.320$; depressed patients versus normal subjects, $t = 0.120$; schizophrenic patients versus normal subjects, $t = 0.430$. These values are in agreement with those of Stotz and Bessey,⁵ who found that the lactate pyruvate ratios for depressed and schizophrenic patients did not differ significantly from the ratio found for normal subjects.

*Lactic and Pyruvic Acids and Their Ratio for Normal Controls and for Patients with Either Depression or Schizophrenia Before and After Intravenous Administration of 250 Mg. of Sodium Amytal **

	Number of Subjects	Lactic Acid, Mg./100 Cc.	Pyruvic Acid, Mg./100 Cc.	Ratio Lactic Acid : Pyruvic Acid
Before sodium amytal				
Normal controls.....	12	6.85 ± 0.64	0.975	7.04 ± 0.86
Depressed patients....	15	8.45 ± 1.14	1.170	7.23 ± 0.93
Schizophrenic patients	12	8.00 ± 0.98	1.050	7.63 ± 0.82
After sodium amytal				
Normal controls.....	3	8.07	0.920	8.61 ± 1.27
Depressed patients....	9	8.40	1.220	6.92 ± 0.42
Schizophrenic patients	8	8.65	0.980	8.89 ± 1.12

* Values are given as means or as means and standard errors.

Our values for lactic acid, however, were considerably lower than theirs, probably owing to the difference in methods used and the fact that our patients were kept under basal conditions.

The absolute values for lactic acid of the blood before administration of the sodium amytal were lower for the normal controls than for either group of patients, but the t values (depressed versus schizophrenic patients, $t = 0.318$; depressed patients versus normal subjects, $t = 1.300$; schizophrenic patients versus normal subjects, $t = 0.982$) indicate that these differences were not significant ones.

Values for the lactate: pyruvate ratio before and after administration of sodium amytal for each group of patients were not significantly changed (before and after administration of sodium amytal for depressed patients, $t = 0.304$; before and after administration of sodium amytal for schizophrenic patients, $t = 0.422$; before and after administration of sodium amytal for normal controls, $t = 1.027$).

9. Values for Fisher's t greater than 2.0 are significant.

COMMENT AND CONCLUSIONS

From these data, it would appear that the lactic and the pyruvic acid contents of venous blood and their ratio do not differ significantly for patients with either depression or schizophrenia from the values for normal controls under basal conditions. The data, furthermore, suggest that the intravenous administration of sodium amytal in a dosage of 250 mg. is not sufficient to change significantly any of these values. This experimental approach does not assist, therefore, in the elucidation of the differential response of the two groups of patients to this drug.

Although there is no essential difference in the general condition of the oxidative reactions as so determined among the two groups of patients and the normal controls, the possibility of other metabolic disturbances is not eliminated. The data simply suggest that general metabolic disturbances may be sought either before or after the pyruvate:lactate phase in the carbohydrate oxidation-reduction system. Neither is the possibility of more specific metabolic disturbances in the central nervous system eliminated. For such studies, blood should be obtained from both the carotid artery and the jugular vein.

The values for the lactic acid of the blood here reported are lower than those recorded elsewhere in the literature, probably as the result both of the method used and of the basal state of the subjects.

Medical Laboratories, Iowa State Psychopathic Hospital.

THE ELECTROENCEPHALOGRAM IN ENCEPHALITIS

F. A. GIBBS, M.D.

AND

E. L. GIBBS

CHICAGO

CURIOUSLY little has been written about the electroencephalographic changes found in association with encephalitis. A report of 1 case was published by Lindsley and Cutts,¹ and the "Atlas of Electroencephalography"² contains figures and several references to this subject. A more extensive report was published by Ross,³ but it was based on only 4 cases. Since encephalitis is a clinical condition of major importance, and since some of the most definite abnormalities that are seen in electroencephalography are encountered in patients with this condition, it seems appropriate to report on a larger number of cases.

MATERIAL AND METHOD

This investigation is based on 240 cases of a disorder clinically diagnosed as encephalitis, studied in different phases of the disease. Ideally it would be desirable to base such a survey on longitudinal data and on electroencephalograms prior to infection; but, for obvious reasons, this is exceedingly difficult if not impossible. Ideal conditions have been only roughly approximated by combining longitudinal and cross sectional data and by assuming that the patient's electroencephalogram prior to infection was normal. Twenty-seven cases were studied during the acute phase of the disease, and repeat electroencephalograms were obtained in the subsequent subacute phase in 8 of these. Twenty-five additional cases were studied in the subacute phase, to bring the total in the subacute group to 33. Electroencephalograms were obtained in 180 cases in the postacute phase; 5 of these were cases in the subacute group in which repeat studies were made. The various etiologic factors represented in the series are shown in table 1, as well as the phases in

From the Department of Psychiatry, University of Illinois College of Medicine.

1. Lindsley, D. B., and Cutts, K. K.: Clinical and Electroencephalographic Changes in Child During Recovery from Encephalitis, *Arch. Neurol. & Psychiat.* **45**:156-161 (Jan.) 1941.

2. Gibbs, F. A., and Gibbs, E. L.: *Atlas of Electroencephalography*, Cambridge, Mass., Lew A. Cummings, 1941.

3. Ross, I. S.: Electroencephalographic Findings During and After Acute Encephalitis and Meningoencephalitis, *J. Nerv. & Ment. Dis.* **102**:172-182 (Aug.) 1945.

which the studies were made. The age distribution of the patients in the post-acute phase is shown in table 2. Electroencephalograms were recorded on a six channel Grass electroencephalograph with monopolar leads from the frontal, parietal, occipital and temporal areas. The indifferent lead was formed by interconnected electrodes on both ear lobes.

RESULTS

In the 27 cases in which the electroencephalogram was obtained in the acute phase of the encephalitis (table 1), slow waves of very

TABLE 1.—*Diseases Acting as Etiologic Factor in 240 Cases of Encephalitis*

Etiologic Disease or Agent	Acute Stage, No. of Cases	Subacute Stage, No. of Cases	Postacute Stage, No. of Cases
Undetermined.....	10	11 (3*)	91 (2 †)
Influenza.....	11	11 (3*)	35 (1 †)
Measles.....	3	2 (1*)	14
Whooping cough.....	0	0	9
Pneumonia.....	2	4 (1*)	10 (1 †)
Mumps.....	0	1	3 (1 †)
Scarlet fever.....	0	0	6
Osteomyelitis.....	1	0	3
Typhoid.....	0	1	1
Mastoiditis.....	0	0	2
Smallpox vaccine.....	0	1	0
Herpes.....	0	0	1
Rheumatic fever.....	0	1	1
Diphtheria vaccine.....	0	0	1
Botulism.....	0	0	1
Sinusitis.....	0	1	0
Chickenpox.....	0	0	1
Otitis media.....	0	0	1
Total number.....	27	33 (8*)	180 (4 †)(1 ‡)

* Patients studied in acute and subacute stages.

† Patients studied in subacute and postacute stages.

‡ Patients studied in acute through postacute stage.

TABLE 2.—*Age Distribution in 180 Cases of Encephalitis in Postacute Phase*

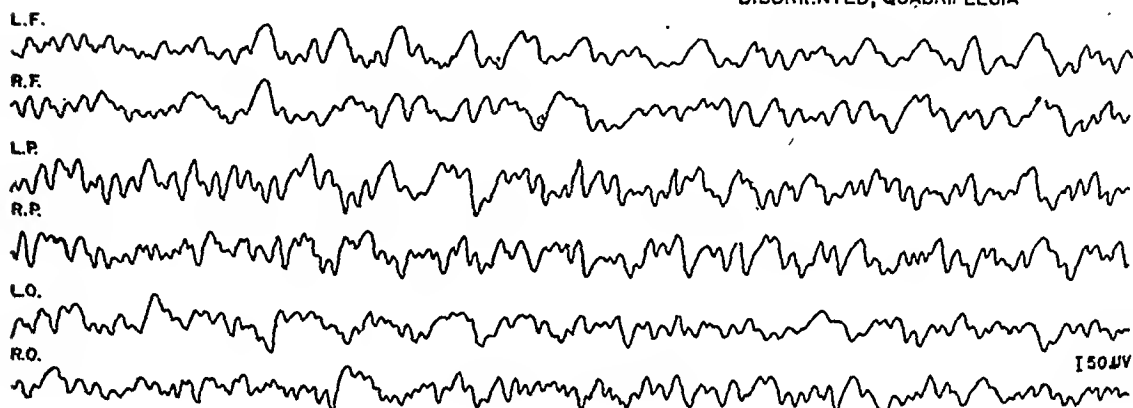
	Age, Yr.						
	0-5	6-10	11-15	16-20	21-30	31-40	41+
With seizures.....	29	16	15	13	12	6	5
Without seizures.....	5	7	7	10	23	16	11

high voltage were apparent. Examples of this type of activity are shown in figures 1 and 2. The slowing was in some cases focal, in others generalized. If the clinical disorder increased in severity, the electroencephalogram became more abnormal, showing still higher voltage and slower waves. In 33 cases studied in the subacute phase (table 1) the electroencephalogram tended to be less abnormal, with

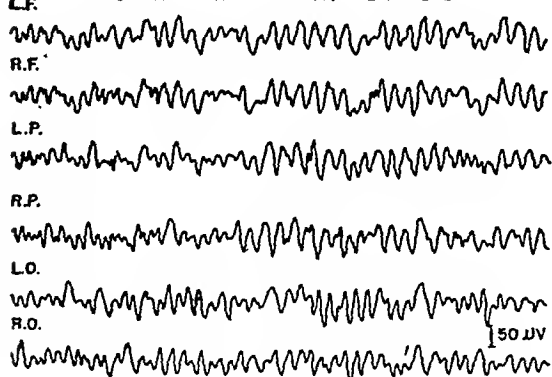
scattered slow waves and with much interposed normal activity (figs. 1 and 2). In cases without seizures the electroencephalogram tended to return to normal during the postacute phase (figs. 1 and 5). However, in some cases, as illustrated in figure 2, it remained slightly abnormal after the patient was free of symptoms (fig. 2).

In the cases in which clinically evident seizures developed in either the subacute or the postacute phase the electroencephalogram was likely to show interseizure discharges of the same type as are commonly

DISORIENTED, QUADRIPLÉGIA



1 MONTH LATER MOTOR WEAKNESS



2 MONTH LATER PARAESTHESIA

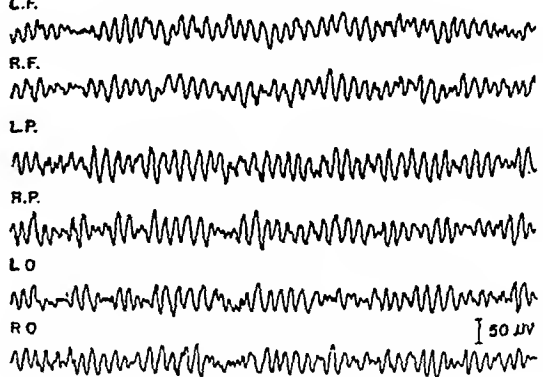


Fig. 1.—Electroencephalograms in a patient aged 42 with encephalitis complicating influenza.

encountered in immediate association with clinical seizures (fig. 3). Three per second activity of the classic petit mal type was common. It was of interest to attempt to determine whether any difference exists between the interseizure electroencephalograms of patients with convulsions and of those without convulsions. In figure 4 the entire series was divided into two groups: cases in which clinical seizures occurred and cases in which clinical seizures did not occur. These groups were

further subdivided according to the electroencephalographic classification. During the acute phase there was no electroencephalographic difference between the two clinical groups. During the postencephalitic phase the electroencephalograms in the cases in which seizures did not occur were normal for the most part, the exceptions being only those in which the electroencephalograms showed slightly slow activity. Only 1 per cent of those in the postencephalitic phase without epilepsy had seizure discharges; yet this group was far from asymptomatic. Some had

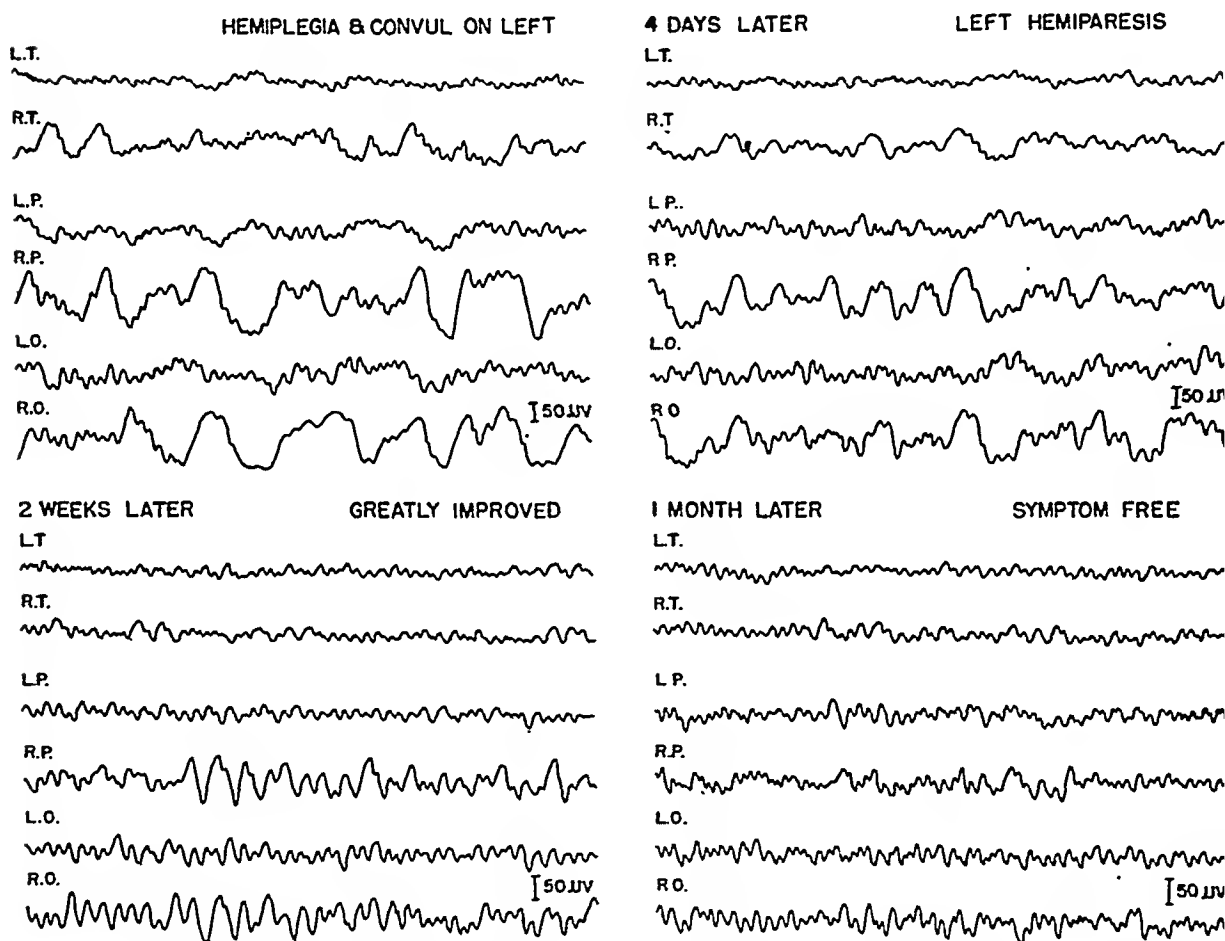


Fig. 2.—Electroencephalograms at various stages of encephalitis in a child aged 10.

paralysis agitans, while others had such symptoms as oculogyric crises and narcolepsy (table 3). Their electroencephalograms, nevertheless, tended to be normal. On the other hand, 58 per cent in the postencephalitic phase with epilepsy had paroxysmal electroencephalograms, i. e., manifest seizure discharges (fig. 3). Thus, only those patients in the postencephalitic phase who had seizures showed a high incidence of electroencephalographic abnormalities.

It would appear from the present data that convulsions are a much commoner postencephalitic symptom in children than in adults (table 2). This observation is in accord with general experience that increasing age gives increasing protection against seizures. As will be seen from table 4, the incidence of focal electroencephalographic abnormality is much higher in the present series of cases of postencephalitic epilepsy than in a group of cases of undifferentiated epilepsy.⁴ In this

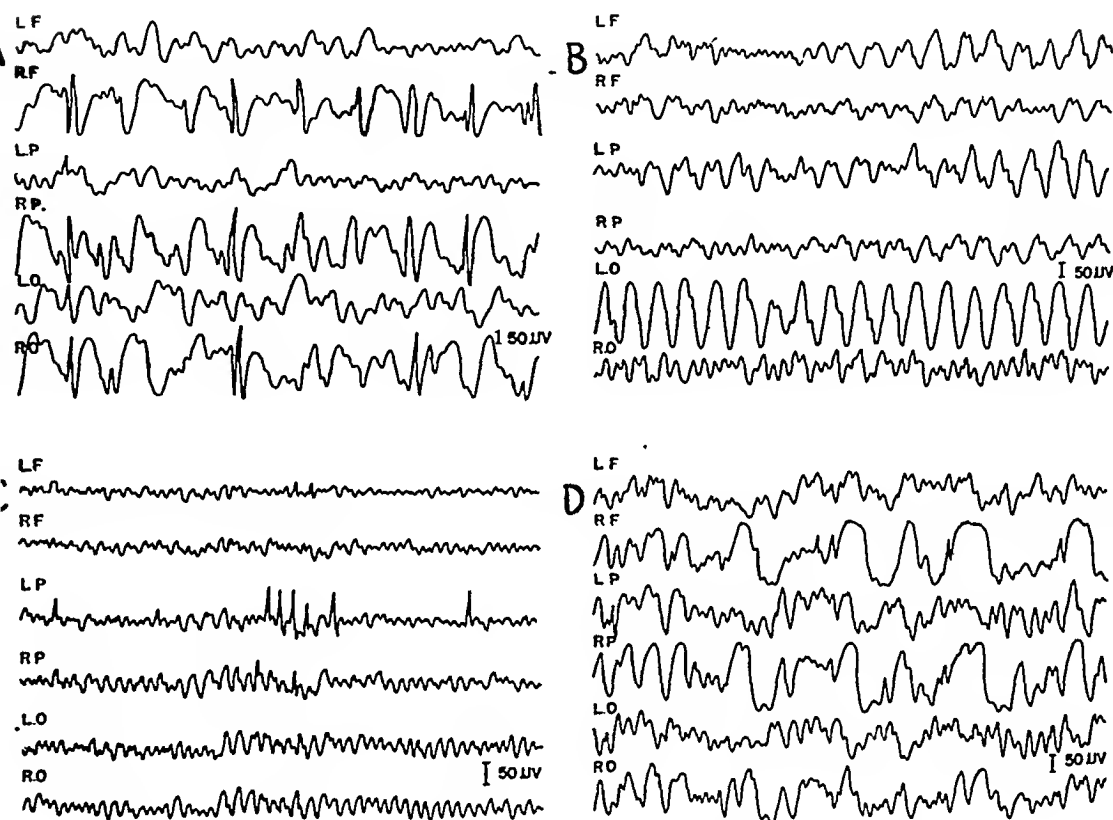


Fig. 3.—Electroencephalograms in 4 cases of postencephalitis with clinical seizures, showing interseizure discharges similar to discharges during seizures. *A*, child aged 4 years, with grand mal and petit mal seizures complicating encephalitis which followed measles; *B*, child aged 9, with grand mal and petit mal seizures complicating encephalitis which followed whooping cough; *C*, child aged 10, with jacksonian seizures occurring during encephalitis following influenza; *D*, child aged 14, with encephalitis of undetermined origin, with grand mal and focal signs.

subgroup of cases of postencephalitis with seizures focal electroencephalographic abnormalities are commoner than focal neurologic signs.

4. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, *Arch. Neurol. & Psychiat.* 50:111-128 (Aug.) 1943.

Examples of electroencephalographic foci in cases of postencephalitic epilepsy are shown in figure 3.

COMMENT

Figures 4 and 5 show that in the subacute and postacute phases of encephalitis the electroencephalogram can be given prognostic significance. The situation is much like that found with severe head

TABLE 3.—*Symptomatic Classification of Cases in Postacute Stage of Encephalitis Without Seizures*

Symptom	No. of Cases
Narcolepsy.....	24
Narcolepsy and cataplexy.....	14
Paralysis agitans.....	17
Oculogyric crises.....	3
Dizzy spells.....	3
Behavior disorder.....	7
Paresthesia.....	3
No symptom.....	3
Weakness of arm or leg.....	2
Unilateral paralysis agitans.....	2
Restlessness.....	1
Sleep walking.....	1
Strabismus.....	1
Mental impairment.....	1
Dysarthria.....	1
Headaches.....	1

TABLE 4.—*Percentages of Focal Encephalographic Abnormality and Focal Neurologic Signs for Patients with Postencephalitic Epilepsy Compared with Percentages for Patients with Undifferentiated Epilepsy*

Clinical Group	Focal Electro-encephalogram	Focal Neurologic Signs
Postencephalitic epilepsy (96).....	65%	45%
Undifferentiated epilepsy (1,000).....	14%	9%

injury,⁵ in which practically all patients show abnormal electroencephalograms but with the passage of time the electroencephalograms of those who are not going to have seizures tend to return to normal, whereas the electroencephalograms of those who are going to have seizures either remain abnormal or after slight improvement become increasingly abnormal. That the same statement holds for encephalitis is indicated in figure 5, in which the incidence of very abnormal electroencephalograms (paroxysmal, very slow or very fast) in the

5. Gibbs, F. A.; Wegner, W. R., and Gibbs, E. L.: The Electroencephalogram in Post-Traumatic Epilepsy, *Am. J. Psychiat.* 100:738-749 (May) 1944.

groups with and without seizures is plotted against the time course of the disease.

From figures 4 and 5 certain diagnostic and prognostic interpretations are possible; for example, if the electroencephalogram is found

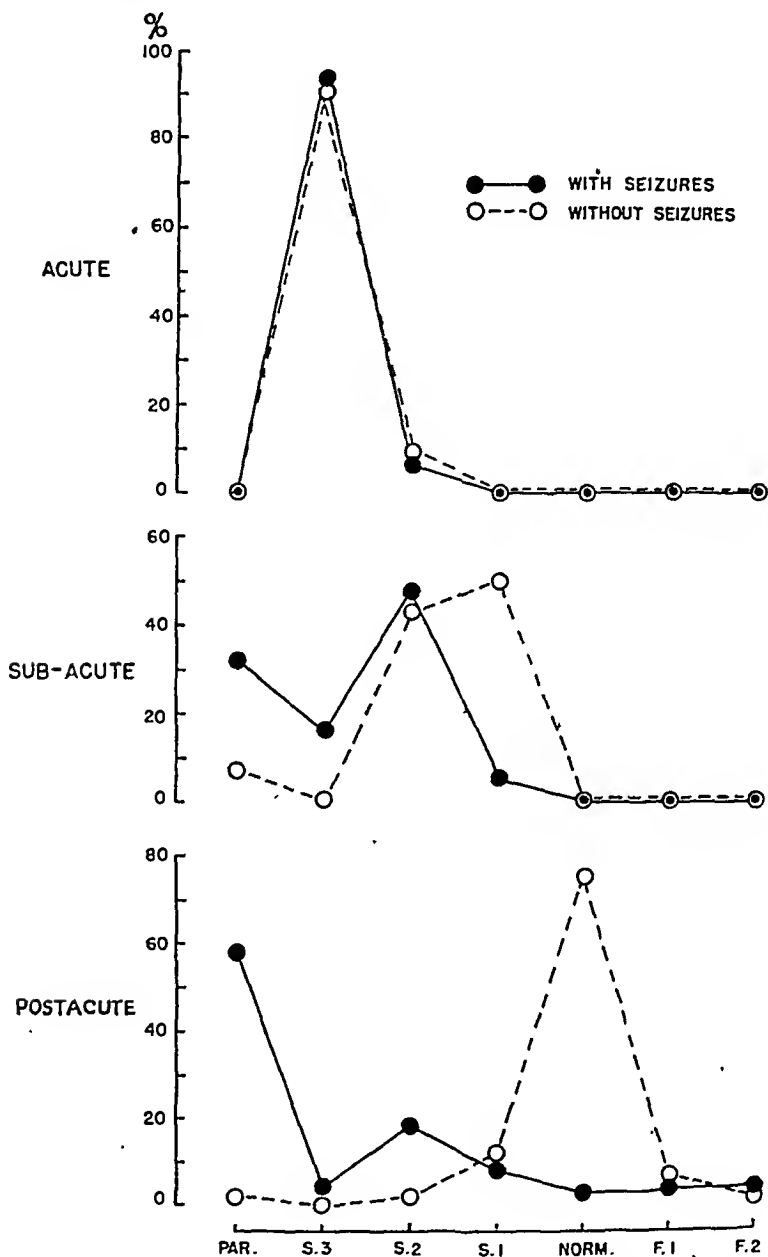


Fig. 4.—Incidence of abnormal electroencephalograms in 240 cases of encephalitis in various phases, divided on the basis of the occurrence of seizures and on the electroencephalographic classification.

to be normal or slightly abnormal during what is supposed to be the acute or the subacute phase of encephalitis, the question should arise

as to whether the clinical diagnosis is correct, for a normal electroencephalogram was never found during the acute or subacute phase in cases of this series and in the great majority of cases it was exceedingly abnormal. In patients with multiple sclerosis who present symptoms suggesting acute encephalitis the electroencephalogram is commonly normal.⁶ A paroxysmal or exceedingly slow electroencephalogram (S-3) after the acute phase is over creates a presumption that the patient will have convulsions and raises a question of the desirability of starting anticonvulsant medication to prevent this development. In the subacute phase a slightly slow electroencephalogram carries a good prognosis for the nonoccurrence of convulsions.

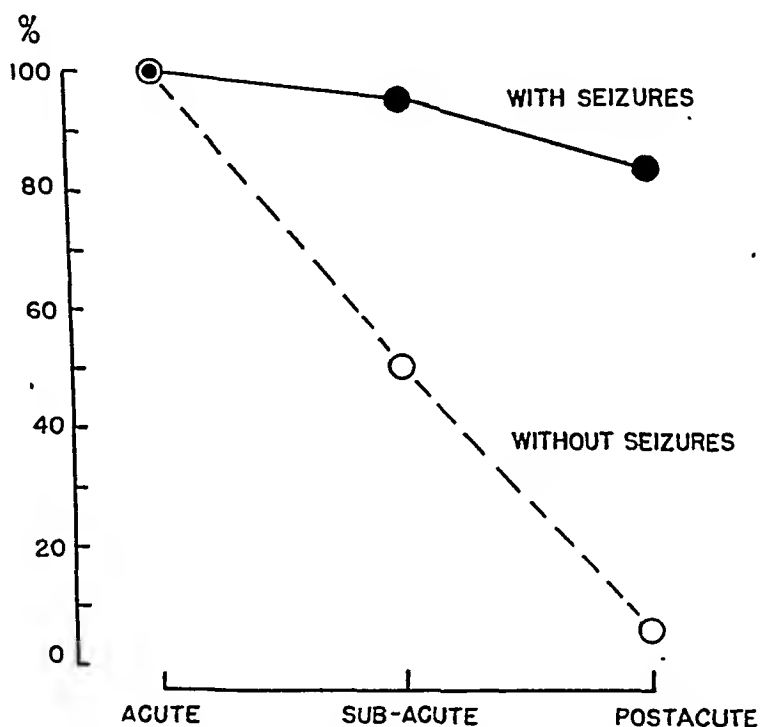


Fig. 5.—Incidence of abnormal electroencephalograms plotted against the phase of the disease for patients with convulsions and those without convulsions.

The high incidence of discharges of the petit mal type in patients with postencephalitic epilepsy contrasts with the rarity of such discharges in cases of epilepsy resulting from birth injury.⁷ This difference might result from a difference in the nature of the injury or its location.

6. Hoefer, P. F. A., and Guttman, S. A.: The Electroencephalogram in Multiple Sclerosis, *Tr. Am. Neurol. A.* **70**:70-73, 1944.

7. Perlstein, M.; Gibbs, E. L., and Gibbs, F. A.: Electroencephalogram in Cerebral Palsy, *A. Research Nerv. & Ment. Dis., Proc.* (1946), to be published.

SUMMARY AND CONCLUSIONS

The electroencephalograms in 240 cases of encephalitis were studied in various stages of the disease. It was found that abnormality is often focal and that it correlates with the stage of the disease. During the acute and subacute phases it correlates with the general severity of symptoms. However, the only feature of the postencephalitic syndrome which correlates highly with electroencephalographic abnormality is the presence of convulsions.

The electroencephalogram has diagnostic value for encephalitis, and after the acute phase is past it has prognostic value for postencephalitic epilepsy.

Wave and spike activity of the petit mal type is a common sequel of encephalitis in children.

University of Illinois College of Medicine.

EFFECT OF ELECTRICALLY INDUCED CONVULSIONS ON PERIPHERAL VENOUS PRESSURE IN MAN

MARK D. ALTSCHULE, M.D.

WOLFGANG M. SULZBACH, M.D.

AND

KENNETH J. TILLOTSON, M.D.

WAVERLEY, MASS.

NEITHER the mechanisms underlying the beneficial effects of electric shock therapy nor the factors responsible for some of the untoward results of that procedure are well understood. Pronounced changes in the physiology of the body as a whole occur during convulsions, and it is therefore important to study them. A recent report by Silfverskiöld and Åmark¹ described changes in venous pressure during electrically induced convulsions in man. It seemed desirable to make a further analysis of the changes observed, and the present report records the results of such a study.

MATERIAL AND METHODS

Fifty-five determinations were made on 12 patients, who ranged in age from 18 to 59 years; 11 subjects were women. The direct method of Moritz and von Tabora² was used. A no. 18 or 19 gage needle was inserted into an antecubital vein, and readings were taken until a base line was reached, usually in two or five minutes. The convulsion was then induced; during and after the convulsion the arm used for the measurements was kept extended by means of manual restraint applied well below the point of insertion of the needle. In only 2 of the 55 experiments was the needle dislodged from the lumen of the vein during the convulsion. Readings were made every fifteen seconds after the electric shock and were discontinued when a base line was reached or, in a few cases, when the patient went into a state of postconvulsive excitement.

From the Clinical Services of the McLean Hospital, Belmont, Mass.; the Medical Research Laboratories of the Beth Israel Hospital, Boston, and the Departments of Psychiatry and Medicine of the Harvard Medical School, Boston.

1. Silfverskiöld, B. P., and Åmark, C.: Disturbance of Circulation in Convulsions of the Epileptic Type: II. Arterial and Venous Pressure During Electroshock, *Acta med. Scandinav.* **113**:191, 1943.

2. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* **98**:475, 1910.

OBSERVATIONS

The initial values for venous pressure lay between 0 and 13 cm. of water and averaged 5.7 cm.; only 4 of the 55 readings were above 10 cm. of water.

During the convulsive seizure the antecubital venous pressure rose to between 35 and 87 cm. of water; in 3 instances the rise was to less than 50 cm., and in 6 it was above 80 cm. The average rise was 63 cm., or 57 cm. above the average control level. The rise reached its maximum during the first fifteen seconds after the shock in 23 instances, reaching in these cases levels of 45 to 85 cm., the average being 60 cm. In the remaining 32 instances the maximal rise during the convulsion was reached thirty or forty-five seconds after the administration of the electric shock. In these instances rises of 1 to 58 cm. occurred after the first fifteen seconds; only 2 of these increases were more than 20 cm., however; and the average for all was only 12 cm.

After the maximal increase in venous pressure was reached during the convulsion, a subsequent decrease occurred in 30 instances while the seizure continued. The decreases ranged from 3 to 44 cm. and averaged 17 cm. of water.

After the end of the convulsion the venous pressure fell rapidly in all but 4 experiments; in 3 of the latter slight rises of 2, 7 and 1 cm. occurred, and in the fourth an immediate fall of only 1 cm. was noted. In all these instances the resumption of respiration was delayed, and when the usual postconvulsive hyperventilation began the venous pressure fell promptly. The return to a base line at a low level of venous pressure occurred within sixty to ninety seconds after the induction of electric shock, or thirty to sixty seconds after the end of the convulsion itself. The control level, however, was reached in only 1 experiment. In all the other experiments the final venous pressure reading was between 4 and 41 cm. above the control level; in only 5 of these, however, was the final level more than 20 cm. above the control level and in these the patients became somewhat excited after the seizure. The final level was, on the average, 13 cm. above the control reading.

COMMENT

Many observers have described elevation of peripheral venous pressure during exercise or straining,³ the amount varying with the severity

3. (a) Moritz and von Tabora.² (b) Burton-Opitz, R.: Muscular Contraction and the Venous Blood Flow: Venous Pressures, *Am. J. Physiol.* 9:161 and 198, 1903. (c) Sewall, H.: Experiments on Venous Blood Pressure and Its Relation to Arterial Blood Pressure in Man, *J. A. M. A.* 47:1279 (Oct. 20) 1906. (d) Hooker, D. R.: The Effect of Exercise on the Venous Pressure, *Am. J. Physiol.* 28:235, 1911. (e) Schott, E.: Die Erhöhung des Druckes im venösen System bei Anstreng-

of muscular effort. It is of especial interest that several studies have shown that the Valsalva maneuver raises the venous pressure notably, i. e., to levels as high as 50 cm. of water.⁴ Much, or most, of the rise in venous pressure observed in the present study was probably a consequence of violent muscular contractions forcing blood rapidly into the

ung, als Mass für die Funktionstüchtigkeit des menschlichen Herzens, Deutsches Arch. f. klin. Med. **108**:537, 1912. (f) Schneider, E. C.: The Circulation of the Blood in Man at High Altitudes: III. The Effects of Physical Exertion on the Pulse Rate, Arterial and Venous Pressure, Am. J. Physiol. **40**:380, 1916. (g) Bürger, M.: Ueber die klinische Bedeutung des Valsalvaschen Versuchs, München. med. Wchnschr. **68**:1066, 1921. (h) Kroetz, C.: Die Koeffizienten des klinisch messbaren Venedrucks, Deutsches Arch. f. klin. Med. **139**:325, 1922. (i) Villaret, M.; St. Girons, F., and Grellety-Bosviel, D.: La tension veineuse périphérique et ses modifications pathologiques, Presse méd. **31**:318, 1923. (j) Bedford, D. E., and Wright, S.: Observations on Venous Pressure in Normal Individuals, Lancet **2**:106, 1924. (k) White, H. L.: Circulatory Responses to Exercise in Man and Their Bearing on the Question of Diastolic Heart Tone, Am. J. Physiol. **69**:411, 1924. (l) White, H. L.; Barker, P. S., and Allen, D. S.: Venous Pressure Responses to Exercise in Patients with Heart Disease, Am. Heart J. **1**:160, 1925. (m) White, H. L., and Moore, R. M.: Circulatory Response to Static and Dynamic Exercises, Am. J. Physiol. **73**:636, 1925. (n) Meyer, O. O., and Middleton, W. S.: The Influence of Respiration on Venous Pressure, J. Clin. Investigation **8**:1, 1929. (o) Bürger, M.: Kreislauffunktionsprüfungen im Sport, Med. Welt **4**:1639, 1930. (p) Tornquist, H.: Physiologische und klinische Studien über den Armvenendruck, Ztschr. f. d. ges. exper. Med. **81**:227, 1932. (q) Nordenfeldt, O.: Studien über Valsalvas Versuch in seiner Anwendung als "Bürgers Pressdruckprobe," Acta med. Scandinav. **82**:465, 1934. (r) Hoffmann, H., and Baumann, H.: Fortlaufende Venendruckmessungen bei Kreislaufbelastung durch den Valsalva'schen Versuch, Ztschr. f. Kreislaufforsch. **26**:729, 1934. (s) Baumann, H.: Fortlaufende Registrierung des Venendruckes mittels einer Photozelle, Klin. Wchnschr. **14**:306, 1935. (t) Méan, H.: Influence de divers agents, notamment de l'acide carbonique, sur la tonicité des veines périphériques de l'homme, Arch. internat. de physiol. **40**:429, 1935. (u) Schneider, E. C., and Collins, R.: Venous Pressure Responses to Exercise, Am. J. Physiol. **121**:574, 1938. (v) Liedholm, K.: Studien über das Verhalten des Venendruckes beim Valsalvaschen Versuch, Acta med. Scandinav., 1939, supp. 106, p. 1. (w) Nieuwenhuizen, C. L. C.: Der venöse Blutdruck nach Arbeitsleistung, eine Funktionsprüfung der Zirkulation, ibid. **103**:171, 1940. (x) Szekely, P.: Venous Pressure Responses to Exercise, Am. Heart J. **22**:360, 1941. (y) Hamilton, W. F.; Woodbury, R. A., and Harper, H. T., Jr.: Arterial, Cerebrospinal and Venous Pressures in Man During Cough and Strain, Am. J. Physiol. **141**:42, 1944. (z) Chapman, E. M., and Linton, R. R.: Mode of Production of Pulmonary Emboli, J. A. M. A. **129**:196 (Sept. 15) 1945. (a') Winsor, T., and Burch, G. E.: Use of the Phlebomanometer: Normal Venous Pressure Values and a Study of Certain Clinical Aspects of Venous Hypertension in Man, Am. Heart J. **31**:387, 1946.

4. Moritz and von Tabora.² Bürger.^{3g} Kroetz.^{3h} Bedford and Wright.^{3j} Meyer and Middleton.³ⁿ Bürger.^{3o} Tornquist.^{3p} Nordenfeldt.^{3q} Hoffmann and Baumann.^{3r} Baumann.^{3s} Méan.^{3t} Liedholm.^{3v} Hamilton and others.^{3y} Chapman and Linton.^{3z} Winsor and Burch.^{3a'}

veins. Variations in the amount of rise in venous pressure in the same patient at various times are consequent to differences in the violence of the seizure and also to differences in the respiratory level at which the seizure commenced; the maximal intrapulmonary pressure developed during forced expiration depends on the volume of air in the lungs at the beginning of such expiration.⁵ During the seizure the patients are apneic, and the violent contractions of the abdominal and thoracic musculature which have been shown to occur during the seizure⁶ induce a Valsalva phenomenon. Additional evidence as to the nature of the respiratory changes is the fact that variations in blood pressure during electrically induced convulsions¹ resemble closely those of the Valsalva experiment.^{3v} Other factors probably operate. For instance, the changes in blood gases which occur during electrically induced convulsions must also result in elevation of venous pressure. Although asphyxia and anoxia have minor, or inconstant, effects on pressure in the venous system,⁷ increase in the carbon dioxide of the blood elevates it⁸; the rise in carbon dioxide tension of blood during convulsions is appreciable.⁹ Still other mechanisms favoring elevation of venous pressure may be activated by changes in autonomic function which occur during electrically induced convulsions. Patients in such seizures show evidence of increased sympathetic activity, consisting in pallor and piloerection, and it is possible that increased amounts of epinephrine are present in the body at this time. The fact that epinephrine con-

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6. Gordh, T., and Silfverskiöld, B. P.: Disturbance of Circulation in Convulsions of the Epileptic Type: I. Intrathoracic and Intra-Abdominal Pressure During Electroshock, *Acta med. Scandinav.* **113**:183, 1943.

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8. Schneider, E. C., and Truesdell, D.: The Effects on the Circulation and Respiration of an Increase in the Carbon Dioxide in the Blood of Man, *Am. J. Physiol.* **63**:155, 1922. Gollwitzer-Meier, K.: Venöse Rückflussregulierung und Venomotorenfunktion unter dem Einfluss der Kohlensäure, *Ztschr. f. d. ges. exper. Med.* **69**:377, 1930. Méan.^{3t}

9. Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Effects of Electrically Induced Convulsions upon Respiration in Man, *Am. J. Psychiat.* **103**:680, 1947.

stricts veins and elevates venous pressure is well known.¹⁰ It has been stated that persistent marked slowing of the heart induced by vagal stimulation may likewise give rise to increases in venous pressure;¹¹ Méan,^{3t} however, could not demonstrate this effect in man. At any rate, it is probably not a factor in the present study, as vagal slowing of the heart is transitory and at most only moderate in electrically induced seizure.¹² The tendency of the venous pressure to fall toward the end of the seizure in many instances is difficult to explain; it is to be noted that a fall in arterial pressure also occurs at this time.¹ In observations on venous pressure during electrically induced convulsions, Silfverskiöld and Åmark recorded changes which were often twice as great as those found in the present study. This difference is difficult to interpret but may be due to differences in the violence of the seizures induced.

The return of venous pressure toward normal is likewise the result of the action of many factors. One of these is the aspirating action of hyperventilation, which draws blood from the periphery into the thorax.¹³ The importance of this phenomenon is difficult to evaluate in most instances, for the cessation of muscular contractions is usually followed quickly by restoration of respiration. In 4 instances in which apnea persisted, however, it is of interest that the venous pressure remained elevated also and finally decreased with the return of respiratory activity. The sequence of events in these cases suggests that the

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11. Burton-Opitz.^{3b} Plumier.^{7b} Bayliss, W. M., and Starling, E. H.: Observations on Venous Pressures and Their Relationship to Capillary Pressures, *J. Physiol.* **16**:159, 1894. Villaret, M.; St. Girons, F., and Grellety-Bosviel, P.: Réflex oculo-cardiaque et tension Veineuse, *Compt. rend. Soc. de biol.* **86**:1006, 1922.

12. Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Significance of Changes in the Electrocardiogram After Electrically Induced Convulsions in Man, to be published.

13. (a) Kroetz.^{3b} (b) Bedford and Wright.^{3j} (c) Henderson, Y.; Pruice, J., and Haggard, H. W.: Influence of Forced Breathing on the Circulation, *J. Pharmacol. & Exper. Therap.* **2**:103, 1918.

aspirating effect of breathing is the important factor, although it must be borne in mind that the onset of hyperventilation may also cause a decrease in venous pressure by lowering the carbon dioxide content and tension of the blood.^{13c} Failure of the venous pressure to return to the control level after a convulsion in spite of hyperventilation might be explained on the basis of some remaining increase in blood carbon dioxide tension⁹ and possibly also persistence of abnormally great sympathetic activity. The fact that Silfverskiöld and Åmark¹ failed to note the common occurrence of final levels of venous pressure above the control values may be a consequence of the fact that their initial values were too high; i. e., their patients were inadequately relaxed.

Too little is known of the changes in circulatory dynamics during electrically induced convulsions to define the effects of the variations in venous pressure observed. It is known, however, that the pronounced rises in venous pressure observed in electric shock or metrazol convulsions are associated with an increase in cerebrospinal fluid pressure¹⁴; like the venous pressure, the cerebrospinal fluid pressure may remain somewhat elevated after the end of the convulsion.^{14b} It is of interest that rises in the spinal fluid pressure occasionally to levels as high as 1,000 mm. have also been reported in the Valsalva experiment.¹⁵ The cardiac output also shows a transitory decrease at the height of the Valsalva procedure.^{3v} The lowered cardiac output and the increases in venous and cerebrospinal fluid pressures probably result in transitory slowing of the circulation in the brain, or at least partial neutralization of the effects of hypertension and hypercardia in increasing cerebral flow.

The magnitude of the increase in venous pressure observed raises the question as to the possible production of capillary hemorrhages in the brain and elsewhere. This consideration is of considerable importance, for increased capillary fragility is well known to occur in malnutrition and has also been described in elderly or in hypertensive persons.¹⁶ It is to be noted, however, that even in the presence of greatly increased capillary fragility it is necessary to increase the venous pressure to a considerable degree for from five to fifteen minutes in order to produce cutaneous petechiae, whereas the marked venous

14. (a) Silfverskiöld and Åmark.¹ (b) Niketic, B., and Susic, Z.: Bemerkungen über das Verhalten des Liquor cerebrospinalis während des Cardiazolkrampfes, *Arch. f. Psychiat.* **108**:562, 1938.

15. Bürger.^{3g} Nordenfeldt.^{3q} Hamilton and others.^{3v}

16. Schrader, R.: Ueber Veränderungen im Vorhalten der Dichte der Kapillarewandung und deren Nachweis durch das Endothelsymptom, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **34**:260, 1921. Beaser, S. B.; Rudy, A., and Seligman, A. M.: Capillary Fragility in Relation to Diabetes Mellitus, Hypertension and Age, *Arch. Int. Med.* **73**:18 (Jan.) 1944.

hypertension which occurs during electrically induced convulsions is of less than a minute's duration. It is unlikely, therefore, that the changes observed in venous pressure during a short convulsive seizure create much danger of extensive intracerebral hemorrhage. The observation of Silfverskiöld and Åmark¹ that the rises in venous pressure in the jugular vein may at times be of minor degree are not entirely acceptable in view of the difficulties these authors experienced in measuring pressure in that vein.

That the Valsalva maneuver is at times hazardous is well known. Liedholm^{3r} reviewed the material bearing on the untoward effects of that procedure on patients with cardiac disease, and more recently Chapman and Linton^{3z} analyzed its dangers in patients with phlebitis. Modification of the convulsive seizure by means of curare, for instance, greatly reduces the rise in venous pressure which occurs¹⁷; convulsions so modified are apparently equal in therapeutic effect to more violent seizures, and it is therefore clear that the circulatory changes which accompany pronounced rises in venous pressure are not essential to clinical improvement.

SUMMARY AND CONCLUSIONS

Electrically induced convulsions cause marked transitory elevations in venous pressure consequent to muscular straining, the Valsalva phenomenon, increased carbon dioxide tension of the blood and possibly also increased circulating epinephrine. After termination of the seizure the venous pressure remains slightly elevated. It is concluded that the pronounced increases in venous pressure are of such short duration as to create little hazard of inducing intracerebral capillary hemorrhages. That other hazards exist is, however, recognized. It is concluded that the marked rise in venous pressure and the circulatory changes associated with it are not essential to obtaining clinical improvement.

McLean Hospital.

17. Altschule, M. D., and Tillotson, K. J.: Modification by Means of Curare of the Circulatory Changes Occurring During Electrically Induced Convulsions in Man, to be published.

RECURRENT ARACHNOIDITIS IN THE DORSAL SPINAL REGION

J. DOUGLAS FRENCH, M.D.
ROCHESTER, N. Y.

ALTHOUGH information is rapidly accumulating concerning spinal arachnoiditis, confusion still exists regarding many aspects of the diagnosis and prognosis of the disease. Much of this confusion arises from a failure to realize that arachnoiditis may be associated with considerable variation in its etiology, location, pathologic process, individual response and clinical course.¹ The present cases are reported to illustrate in particular the exacerbation-remission type of course frequently seen in patients with spinal arachnoiditis. Such fluctuations in clinical manifestations explain many controversial elements concerning physical changes, abnormalities of the spinal fluid and prognosis.

CLINICAL MATERIAL

The 4 cases presented were selected from 8 cases of dorsal arachnoiditis of the dorsal spinal region studied at the Strong Memorial Hospital. The diagnosis was verified in 2 cases at operation and indicated in the remaining 2 cases by virtue of compatible clinical manifestations and subarachnoid studies.

REPORT OF CASES

CASE 1.—A woman aged 51 had an attack of polyarthritis and "sciatica" on the left side coincident with a severe erysipeloid infection of the left ear twelve years before her first admission to the hospital. Three years before admission a similar attack occurred, supposedly with a bout of tuberculous cervical adenitis. Twelve days before admission—two months following a recurrent infection of the left middle ear—pain and numbness developed in the right hand and arm, followed by numbness of the right side of the trunk and the right leg. Pain and paralysis in the right leg, weakness in the left leg and retention of urine rapidly followed.

At the time of admission she was found to have bilateral chronic infection of the middle ear and deafness. Neurologic examination revealed a questionable weakness of the left side of the face and pronounced but patchy bilateral sensory changes below the eighth cervical dermatome. There was weakness of the right upper extremity and of both lower extremities, amounting to almost complete paralysis of

From the Department of Surgery, Division of Neurosurgery, University of Rochester School of Medicine and Dentistry.

1. Ramsey, G. H. S.; French, J. D., and Strain, W. H., in Pillmore, G. U.: *Clinical Radiology: A Correlation of Clinical and Roentgenological Findings*, Philadelphia, F. A. Davis Company, 1946, pp. 132-134.

the right leg. Deep reflexes were greatly increased throughout, and Babinski's sign was present bilaterally. Lumbar puncture revealed normal manometric readings. The spinal fluid contained 50 mg. of protein per hundred cubic centimeters and 59 leukocytes per cubic millimeter.

A chronically infected left antrum was corrected surgically, and infected teeth were removed.

Eight months later a letter from the patient's physician reported that her sensation, reflexes and muscular power were normal and that she had resumed normal activities.

Approximately one year later, coincident with a streptococcic infection of the throat, she had a similar bout of paraplegic motor and sensory changes. She was said to have been given an autogenous vaccine and to have again almost completely recovered after several months.

About nine months before readmission to the hospital she began to have gradually increasing numbness, spasticity and weakness of both legs and the left arm. There was also increasing bladder difficulty.

On readmission to the hospital, she was found to have marked spasticity with increased deep reflexes and to present Babinski's sign in both lower extremities. Hypesthesia in a glove and stocking distribution was present in the left hand and in both feet. Lumbar puncture revealed normal dynamics, and the protein content of the fluid was 35 mg. per hundred cubic centimeters. A myelogram showed no abnormality. She was discharged unimproved.

Comment.—This patient had five exacerbations of a similar neurologic disease in a period of nineteen years. During two of these illnesses she was studied at the Strong Memorial Hospital. The early episodes were mild and infrequent, but the later attacks were severe and associated with persistent disability. Of particular interest is the fact that during one illness the spinal fluid protein was increased twelve days after onset, whereas seven years later it was normal nine months after another exacerbation. The etiologic factor in this case seems to be significantly associated with infections of the sinuses, ears and teeth.

CASE 2.—A man aged 30 gave a history of bouts of pain in the chest associated with a productive cough. These episodes lasted one week and had occurred over a period of five years prior to his first admission to the hospital, in 1936. One year before his admission a similar episode, lasting ten days, was associated with sphincteric disturbances and weakness in the legs. These symptoms gradually subsided over a period of two months. Two weeks before his admission to another hospital cough and pain in the chest again developed, followed rapidly by weakness and tingling in the legs. He was found to have an inconstant sensory level at the fifth dorsal dermatome, spastic gait, increased deep reflexes of the lower extremity with ankle clonus and absence of the abdominal reflexes. Studies of the subarachnoid fluid were reported to show a partial block and "enormous increase" in spinal fluid protein.

On admission to the Strong Memorial Hospital two weeks later he was found to have patchy sensory changes up to the fifth dorsal dermatome. Spastic weakness with increased deep reflexes were present in the legs, and the abdominal reflexes were absent. The Babinski sign was not present. Lumbar puncture at this time showed a questionable block with a spinal fluid protein reading of 7 mg. per hundred cubic centimeters, and myelographic studies demonstrated a partial

block at the level of the first dorsal vertebra. Surgical exploration at this level revealed cystic arachnoiditis, and the cyst was opened.

After operation the patient was greatly improved, but he returned two months later with a similar, if milder, episode. Lumbar puncture again showed a partial block and the protein content of the fluid was reported to be "moderately increased."

Nine years later he reported by mail that similar episodes of diminishing frequency and intensity occurred at yearly intervals but that he had been completely well for two years.

Comment.—This patient had many attacks of arachnoiditis over a period of fourteen years, supposedly associated with repeated pulmonary infections. In two acute episodes the spinal fluid protein was found to be increased. In one instance the reading was very low two weeks after the protein content had been reported to be "enormously increased." The diminishing severity of attacks, culminating in complete subsidence of symptoms, in this case is contrary to the more frequent progression of symptoms.

CASE 3.—An Italian laborer aged 52 first noted vague pain in the right upper abdominal quadrant two months before admission to the hospital. This became more severe two weeks before admission, was worse on coughing and straining and was of "girdle" type. He also reported some pain and subjective numbness in his fingers and legs. There were a loss of 25 pounds (11.3 Kg.) in weight and a feeling of generalized weakness. The past history revealed that he was known to have had diabetes for three years but was not taking insulin.

On examination the patient appeared chronically ill. Patchy hypesthesia corresponding to the tenth dorsal dermatome was present. Reflexes were absent in the lower extremities, and Babinski's sign was not present. There was weakness of the right abdominal wall on straining as well as weakness of both legs.

A lumbar puncture revealed normal manometric readings, but the fluid had a protein content of 400 mg. per hundred cubic centimeters. Three days later the protein determination showed a level of 100 mg. per hundred cubic centimeters, and a week later it was 15 mg. per hundred cubic centimeters.

The patient was discharged as improved but returned to the hospital two weeks later because of recurrence of symptoms. The physical findings on this occasion were similar to those previously reported but were somewhat more pronounced. He now showed a sensory level as high as the fourth dorsal dermatome, and cutis anserina was occasionally noted in the hypesthetic areas. A lumbar puncture four weeks after the first subarachnoid studies revealed evidence of partial block, and the fluid showed a total protein content of 600 mg. per hundred cubic centimeters. A cisternal myelogram with "pantopaque" (a mixture of ethyl esters of isomeric iodophenylundecylic acids) showed irregularity and fragmentation of the visualized column in the midthoracic region (figure), and the protein content of the cisternal fluid was 15 mg. per hundred cubic centimeters. Exploratory laminectomy was performed at the level of the seventh to the ninth dorsal spine, and a milky, thick arachnoid adherent in many places to an atrophic-appearing cord was encountered. The adhesions were divided so far as was possible.

After operation the patient was given radiation therapy, and when seen six weeks after operation he was much improved and ambulatory but still complained of pain in his legs. He died two years later, apparently of disease of the spinal cord.

Comment.—The most remarkable aspect of this case was the rapid and extensive change demonstrated in the subarachnoid studies. The elevated protein level of the spinal fluid fell and partial subarachnoid block disappeared in a week, only to show reversion to a pathologic state two weeks later. Initial improvement was present after operation,



Myelogram taken with "pantopaque" in case 3, showing irregular appearance of the visualized column in the dorsal region.

but a letter from the patient's wife indicated that he died two years later, apparently from a more severe exacerbation of arachnoiditis.

CASE 4.—A farmer aged 30 was hospitalized eleven years prior to his present admission for drainage of multiple epidural abscesses in the dorsal region. He was paraplegic at the time but recovered to the degree that he could work on

his farm without supporting aid. Two weeks before his admission abdominal pain developed, followed by numbness and spasticity in his legs.

On examination, he was found to have such severe spasticity of both lower extremities that he was just able to get about with crutches. There was bilateral hypesthesia of the calves and feet in stocking distribution. The reflexes were hyperactive in the lower extremities, and the Babinski sign was present bilaterally. Bladder function was impaired. A myelogram obtained with "pantopaque" demonstrated a complete block at the level of the first lumbar vertebra. The spinal fluid protein was 375 mg. per hundred cubic centimeters.

The patient began to improve spontaneously and in ten days was able to get around with considerable freedom. The sensory changes had disappeared, and bladder function was normal. Lumbar puncture at this time revealed normal manometric readings and a spinal fluid protein of 30 mg. per hundred cubic centi-

Data on Subarachnoid Studies

Case No.	Time After Onset of Attack	Protein Content of Fluid, Mg./100 Cc.	Manometric Observations	Myelographic Observations
1	2 weeks	50	No block	No abnormality
	9 months (subsequent attack)	35	No block	
2	2 weeks	"Enormously increased"	Partial block	Partial block first dorsal level
	4 weeks	7	Questionable block	
	1 week (subsequent attack)	"Moderately increased"	Partial block	
3	2 months	400	No block	Irregularity in dorsal region
	10 days later	15	No block	
	3 weeks later	600	Partial block	
4	2 weeks	375	Complete block	Complete block at first lumbar level
	4 weeks	30	No block	

meters. Three months later his condition had improved still more but he had not regained full use of his legs.

Comment.—This patient had an acute exacerbation and remission of spinal arachnoiditis eleven years after operation for epidural abscesses in the dorsal region. The rapid transformation of subarachnoid block and high spinal fluid protein to a normal state seen in case 3 was present here. The associated clinical improvement was initially striking, although it was not yet complete three months later.

GENERAL COMMENT

The clinical course of spinal arachnoiditis in most instances is characterized by exacerbation and remission of symptoms.² Later, exacerba-

2. Howell, C. M. H.: Arachnoiditis: President's Address, Proc. Roy. Soc. Med. 30:33-42 (Nov.) 1936. Vincent, C.; Puech, P., and David, M.: Sur le diagnostic, le traitement chirurgical, le pronostic des arachnoïdites spinales, Rev. neurol. 1:577-595 (April) 1930.

tions may produce neurologic residua suggesting a chronic progressive disease. It is possible at this stage that limiting adhesions or vascular involvement may cause increasing deterioration of the spinal cord,³ but clinical evidence supports the intermittent nature of the actual inflammatory process. Normal manometric readings and normal protein contents of the spinal fluid may be encountered, therefore, in patients with advanced neurologic changes due to arachnoiditis. Conversely, high protein readings and various degrees of subarachnoid block may be present a few days after the onset of the disease in previously perfectly well persons.

The cases of dorsal spinal arachnoiditis reported here clearly demonstrate the rapid changes which may take place in the subarachnoid system coincident with fluctuation in symptoms. In case 1 no block or alteration in protein was encountered in spite of evidence of advanced involvement of the spinal cord. The patient had experienced a rather severe exacerbation nine months previously, and irreversible changes had obviously occurred in the spinal cord. The other 3 patients, however, were examined during the acute phase of the disease and showed pronounced abnormality in subarachnoid pressure and in the spinal fluid. There is indication, therefore, that spinal arachnoiditis is an acute recurrent process. It becomes chronic only when organized adhesions or cysts have formed, producing irreversible changes in the spinal cord. Changes in subarachnoid pressure and in the spinal fluid appear to follow promptly these fluctuations in symptoms.

Spinal arachnoiditis in the region of the cauda equina has been shown to follow a course of exacerbations and remissions similar to that illustrated here in dorsal arachnoiditis.⁴ Involvement of the cauda equina is, in fact, much more common than dorsal or cervical inflammations of this type.

It is of note that "cystic arachnoiditis" was observed at operation in 1 of the verified cases in this group and "adhesive arachnoiditis" in the other. The clinical manifestations, however, were strikingly similar. It is likely that the different types of arachnoiditis described are really only variations of the same process.

In considering the various clinical alterations produced by spinal arachnoiditis, particular attention must be directed to the stage of the disease with which the examiner is involved. Failure to recognize this important point is undoubtedly responsible for the disagreement apparent in available discussions of the subject. The same considerations must be recognized in evaluating the efficiency of various types of therapy and in assigning a prognosis in individual cases.

3. Stookey, B.: Adhesive Spinal Arachnoiditis Simulating Spinal Cord Tumor, *Arch. Neurol. & Psychiat.* **17**:151-178 (Feb.) 1927.

4. French, J. D.: Clinical Manifestations of Lumbar Spinal Arachnoiditis, *Surgery* **20**:718-729 (Nov.) 1946.

The similarity of spinal arachnoiditis and other diseases characterized by albuminocytologic dissociation frequently makes differentiation impossible.⁵ Further clinical and pathologic observations are necessary to record the actual interrelationship of diseases of this group.

SUMMARY

Four cases of dorsal spinal arachnoiditis are presented in which exacerbation and remission over long periods characterized the course of the disease.

Rapid and repeated changes in subarachnoid block and protein content of the spinal fluid occurred coincident with the recurrence of clinical symptoms.

Such fluctuation in clinical manifestations is the basis for disagreement concerning many aspects of spinal arachnoiditis.

University of Rochester School of Medicine and Surgery.

5. Casamajor, L., in discussion on Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: *Polyneuritis: A Clinical and Pathological Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis*, Arch. Neurol. & Psychiat. 35:937-963 (May) 1936.

SCHISTOSOMIASIS JAPONICA WITH INTRACEREBRAL GRANULOMA; OPERATIVE REMOVAL WITH RECOVERY

Report of a Case

DAVID L. REEVES, M.D.*

SANTA BARBARA, CALIF.

AND

RUSSELL W. KERR, M.D.†

KANSAS CITY, MO.

SCHISTOSOMIASIS japonica, or Oriental schistosomiasis, being limited to foci in Japan, Formosa, China, the Philippines and the Celebes, is rarely seen in this country. Cerebral symptoms and manifestations of this infection are experienced even more uncommonly.

The first of such cases was published in 1906 by Tsunoda and Shimamura.¹ Their patient experienced indigestion and abdominal pain in 1901, began to have convulsive seizures with loss of consciousness and aphasia in 1903 and, after a series of right-sided convulsions, presented a right hemiplegia. Autopsy, in August 1904, revealed diffuse thickening of the cerebral meninges, with abnormal masses in the left parietal region, partly in the gray and partly in the white matter, as well as a zone of softening involving the internal capsule, the optic thalamus and the basal ganglia on the left side. The ova were also discovered in the choroid plexus and the spinal cord.

In 1935 Nieva² described the symptoms of a patient from Borongan, Samar, who complained of generalized numbness, dizziness, headache and convulsive episodes, accompanied with loss of consciousness. The feces

* Formerly Colonel, Medical Corps, Army of the United States.

† Formerly Major, Medical Corps, Army of the United States.

From the Neurosurgical and Laboratory Services of Hammond General Hospital, Modesto, Calif.

Read at the combined meeting of the medical and surgical staffs of Hammond General Hospital Oct. 12, 1945; at the staff meeting of the Santa Barbara Cottage Hospital June 24, 1946, and at the meeting of the American Academy of Neurological Surgery, Hot Springs, Va., Sept. 11, 1946.

1. Tsunoda, T., and Shimamura, S.: Beiträge zur pathologischen Anatomie der sogenannten Katayama-Krankheit, zur Aetiologie der Hirngefäßembolie und der Jackson'schen Epilepsie, Wien. med. Wchnschr. 56:1681, 1906.

2. Nieva, D. E.: Epileptiform Convulsions Probably Due to Schistosomiasis, Bull. San Juan de Dios Hosp., 1935, no. 7, p. 9.

of the patient contained the ova of *Schistosoma japonicum*, and the diagnosis of probable cerebral schistosomiasis was made by inference from the fact that the patient improved with injections of antimony potassium tartrate and emetine hydrochloride.

In 1936 Africa, de Léon and Garcia³ reported a case in which the ova were associated with a fatal hemorrhage into the right basal ganglia of the brain. During the same year Egan⁴ described cerebral symptoms and neurologic abnormalities in 2 of his 12 cases in which improvement followed antimony therapy.

Strangely, some of the recent publications have overlooked the 2 cases in which Mr. Julian Taylor and Sir Percy Sargent performed operation and which were reported by Greenfield and Pritchard⁵ in 1937. In each case an unsuspected granuloma containing the eggs of *S. japonicum* was removed surgically from the left parietal region of the brain, with clinical recovery. The first patient, a lieutenant in the Royal Navy, had a series of epileptic attacks at the age of 30, about four years after having been exposed in China to water endemic for schistosomiasis. Except for an attack of diarrhea, lasting about three weeks, without any recorded febrile disturbance or any irritative cutaneous rash, and the history of exposure, there was nothing to suggest the disease. At the time of his seizures, the patient believed that he was in excellent health. He described a visual aura of flashes of light in the obscured vision of the right peripheral field, and subsequently aphasic symptoms associated with clumsiness in the use of the right hand became evident.

Ventriculographic studies, performed by Mr. Taylor, disclosed narrowing of the left lateral ventricle, with forward displacement of the body and posterior horn, and failure of filling of the left temporal horn. The third ventricle was narrowed and displaced slightly to the right. These observations corroborated the clinical impression of a tumor in the left parieto-occipital region.

Mr. Julian Taylor operated on Jan. 20, 1936, removing a friable, yellow mass from beneath the surface of the brain in the suspected area, and pathologic examination revealed this to be a granuloma containing the eggs of *S. japonicum*. The patient was given a total dose of 30 grains (1.95 Gm.) of antimony tartrate intravenously and made an uneventful recovery. His residual symptoms included grossly defective visual stereognosis in the right visual field and occasional attacks of dizziness

3. Africa, C. M.; de Léon, W., and Garcia, E. Y.: Heterophydiasis: III. Ova Associated with a Fatal Hemorrhage in the Right Basal Ganglia of the Brain, *J. Philippine Islands M. A.* 16:22, 1936.

4. Egan, C. H.: An Outbreak of Schistosomiasis Japonica, *J. Roy. Nav. M. Serv.* 22:6, 1936.

5. Greenfield, J. G., and Pritchard, B.: Cerebral Infection with *Schistosoma Japonicum*, *Brain* 60:361, 1937.

with associated aphasia. Up to June 1937 he had experienced only one episode of unconsciousness, lasting about thirty minutes.

Their second patient, also a lieutenant in the Royal Navy, experienced severe generalized headaches, more pronounced in the left parietal region and associated with occasional morning vomiting. Impaired vision was noted in the right temporal field, and on examination papilledema and right lower quadrantic hemianopsia were discovered. Operation was performed on Sept. 15, 1930 by Sir Percy Sargent, who removed subtotally a large tumor from the upper part of the left parieto-occipital region. This mass revealed a pathologic picture quite similar to that in the first case. Subsequently, the patient was treated with antimony potassium tartrate. At his last reported examination, in June 1931, he stated that he was fairly well. Examination disclosed only right homonymous hemianopsia and slight astereognosis of the right hand.

Interestingly, in neither case was there any symptom to suggest the nature of the infection, and in each operation was performed for supposed glioma.

In 1941 Vitug, Cruz and Bautista⁶ reported 2 cases of schistosomiasis in which cerebral symptoms were produced almost exclusively, with improvement following the use of stibophen ("fuadin"; sodium antimony III bis-catechol-2, 4-disulfonate) in 1 case and with confirmatory necropsy observations in the other.

Billings, Winkenwerder and Hunninen,⁷ in 1946, reported their clinical study of 337 cases of acute schistosomiasis japonica in the Philippine Islands, with the results of stibophen therapy in 110 cases. In 7 cases neurologic symptoms developed, but in only 3 were the manifestations of a severe character, including hemiplegia and other cerebral symptoms. Improvement followed stibophen therapy. In their opinion, the onset of the cerebral symptoms and peripheral neurologic signs, indicating extensive involvement, was so abrupt that it was difficult to believe that the changes were due solely to deposition of ova. Inasmuch as there were simultaneously rather extensive urticaria and angioneurotic edema, the possibility that cerebral edema played a role was considered likely. During the same year, Carroll⁸ described 5 cases of cerebral involvement complicating schistosomiasis japonica; neurologic involvement was apparent in the acute stage of the disease in 4 of these cases and four months after the acute stage in 1 case.

6. Vitug, W.; Cruz, J. R., and Bautista, L. D.: Schistosomiasis Involving the Brain: Two Case Reports, *J. Philippine Islands M. A.* **21**:291, 1941.

7. Billings, F. T.; Winkenwerder, W. L., and Hunninen, A. V.: Studies on Acute Schistosomiasis Japonica in the Philippine Islands: I. A Clinical Study of Three Hundred and Thirty-Seven Cases with a Preliminary Report on the Results of Treatment with Fuadin in One Hundred and Ten Cases, *Bull. Johns Hopkins Hosp.* **78**:21, 1946.

8. Carroll, D. G.: Cerebral Involvement in Schistosomiasis Japonica, *Bull. Johns Hopkins Hosp.* **78**:219, 1946.

As can be appreciated from a review of the literature, only 2 other cases have been reported in which the intracranial granuloma was removed surgically with clinical recovery. For this reason, and because similar experiences may be anticipated subsequently as the result of large numbers of troops having been stationed in infected areas, it is believed important to describe the first experience of this kind in this country.

REPORT OF CASE

History.—In January 1945 a soldier, aged 29, on duty in the Southwest Pacific area, and previously in excellent health, experienced the onset of diplopia, followed by frequently recurring headaches. The diplopia persisted for four months before subsiding, but the headaches continued and increased in severity gradually. Convulsive episodes occurred. The first seizure, in January, led to his hospitalization until March. He was again hospitalized for a week after his second attack, in May, and after his return to the United States he experienced his third convulsion, on Aug. 18, 1945.

The convulsions were preceded by the prodromal symptom of a flash of light, which was not lateralized. No history of biting the tongue or of incontinence was obtained. In the last episode the patient recalled a spasmodic jerking of the left side of the face, but no other detail of the pattern of the attack was noted. After the periods of unconsciousness, the patient recalled no weakness of his extremities or any other lateralizing sign.

The information was obtained of a minor head injury sustained during a blackout in December 1944, while the patient was on an LST, during an invasion of Mindoro Island. There was no unconsciousness or apparent sequela. The past history disclosed nothing else of a contributory character.

Examination.—Because of the probability of an intracranial expanding lesion, the patient was transferred from the Oakland Area Regional Hospital to Hammond General Hospital in Aug. 29, 1945. General physical examination revealed nothing unusual. The patient was mentally alert, cooperative and in no acute distress, although he complained of a constant generalized headache. The temperature, pulse and blood pressure recordings were normal. A complete blood count and urinalysis revealed nothing unusual, and the Kahn reaction of the blood was negative.

Neurologic examination uncovered the following abnormalities: bilateral papilledema; slightly impaired stereognosis on the left side as compared with that on the right, associated with slight weakness of the left hand grip, and a higher-pitched percussion note on the right side of the calvaria than on the left. Ophthalmologic consultation confirmed the presence of bilateral papilledema of approximately 1 D., and normal peripheral fields with enlargement of the blindspots consistent with the papilledema were reported.

Roentgenograms of the chest demonstrated no evidence of pulmonary or cardiac disease, but those of the skull revealed that the calcified pineal body, seen in its normal position in the lateral views, was displaced 1.1 cm. to the left of the midline in the anteroposterior projection. The electroencephalographic recordings, on Sept. 4, 1945, showed predominantly low voltage and fast activity in all leads, with occasional 9 per second activity. No focal signs or responses to hyperventilation were observed. Occipital asymmetry with increased amplitude in the left occipital region was evident.

On September 4 a spinal fluid pressure of 200 mm. was obtained and 15 cc. of clear, colorless fluid removed, which contained 70 mg. of protein per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was 2 plus and the colloidal gold curve 544321110. The second lumbar puncture, on September 10, showed a pressure of 430 mm. of spinal fluid. The small amount of clear, colorless fluid removed contained 1 cell per cubic millimeter; the Wassermann and Kahn reactions were negative; the colloidal gold curve was normal.

In the absence of any history of syphilis or evidence of a penile lesion, it seemed difficult to explain the clinical findings on the basis of syphilis or gumma of the central nervous system, and it was believed that the one positive Wassermann reaction of the spinal fluid represented a false positive one. The clinical impression was that of an intracranial expanding lesion in the right temporo-occipital area, and because of the history of a previous minor head injury the possibility of a subdural hematoma was entertained.

In spite of the localizing clinical signs, it was believed advisable to precede operative intervention with a ventriculographic study, and this was performed on September 19, with the use of local anesthesia. Approximately 20 cc. of air was injected and a similar amount of ventricular fluid removed from the posterior horn of the left ventricle. The ventriculograms revealed shifting of the well filled ventricular system to the left side, and this included a similar displacement of the third ventricle. There was a noticeable filling defect of the posterior and temporal portions of the right lateral ventricle, which appeared flattened and depressed. It was believed that these changes confirmed the impression of an expanding lesion in the right temporo-occipital region.

Operation and Diagnosis.—With anesthesia induced with solution of tribromoethanol U. S. P. and ether, a small osteoplastic craniotomy flap was turned down in the right occipitoparietal region in the usual manner. The bone in the subtemporal region was rather thin. A small portion of bone in this region was removed for decompression. The dura, which was tense, was opened in the posterior portion of the operative field to uncover tumor tissue overlying the corresponding area of the cortex. Small, whitish tubercles, from a pinpoint to a pinhead in size, were noted on the surface of the tumor; and as the indurated and rubbery tumor was removed piecemeal, it was observed to contain small calcified areas, but no caseation was apparent. The tumor tissue seemed to extend in a cluster, or racemose-like arrangement of granulomatous material, the portions varying in size. With removal of all this tissue, which extended into the subtemporal region and comprised a mass the size of an orange, the intracranial pressure was relieved. The nature of the granuloma was not determined at this time, and it was the operator's impression that the tumor was an unusual type of glioma which allowed nothing further to be accomplished surgically.

At first the diagnosis of the removed tumor was puzzling. Its similarity to both a tuberculoma and a gumma was misleading, and only after additional study and examination was the unusual and unexpected diagnosis of schistosomiasis japonica arrived at.

Pathologic Report.—The specimen consisted of many moderately firm pieces of grayish, mottled tissue, the largest measuring 3.0 cm. in maximum diameter. The pieces of tissue were tough and rubbery, showed no definite architecture but had numerous grayish areas of necrosis. On section, one portion of the specimen presented a homogeneous, grayish, glistening surface, was quite firm and in various planes had lighter grayish lines running through it. Sections of most of the pieces, however, disclosed a yellowish area of caseous-appearing necrosis scattered irregularly throughout.

A frozen section revealed areas of caseous necrosis and inflammatory cells. All the cysts were apparently lost in cutting, for none was observed in the frozen section material, either with the rapid methylene blue stain or with the hematoxylin and eosin stain.

The paraffin section presented a striking picture, with some of the oval cystic structures appearing in nearly every field. Careful search was necessary, however, to find any with spines sufficiently characteristic to be of value in determining the

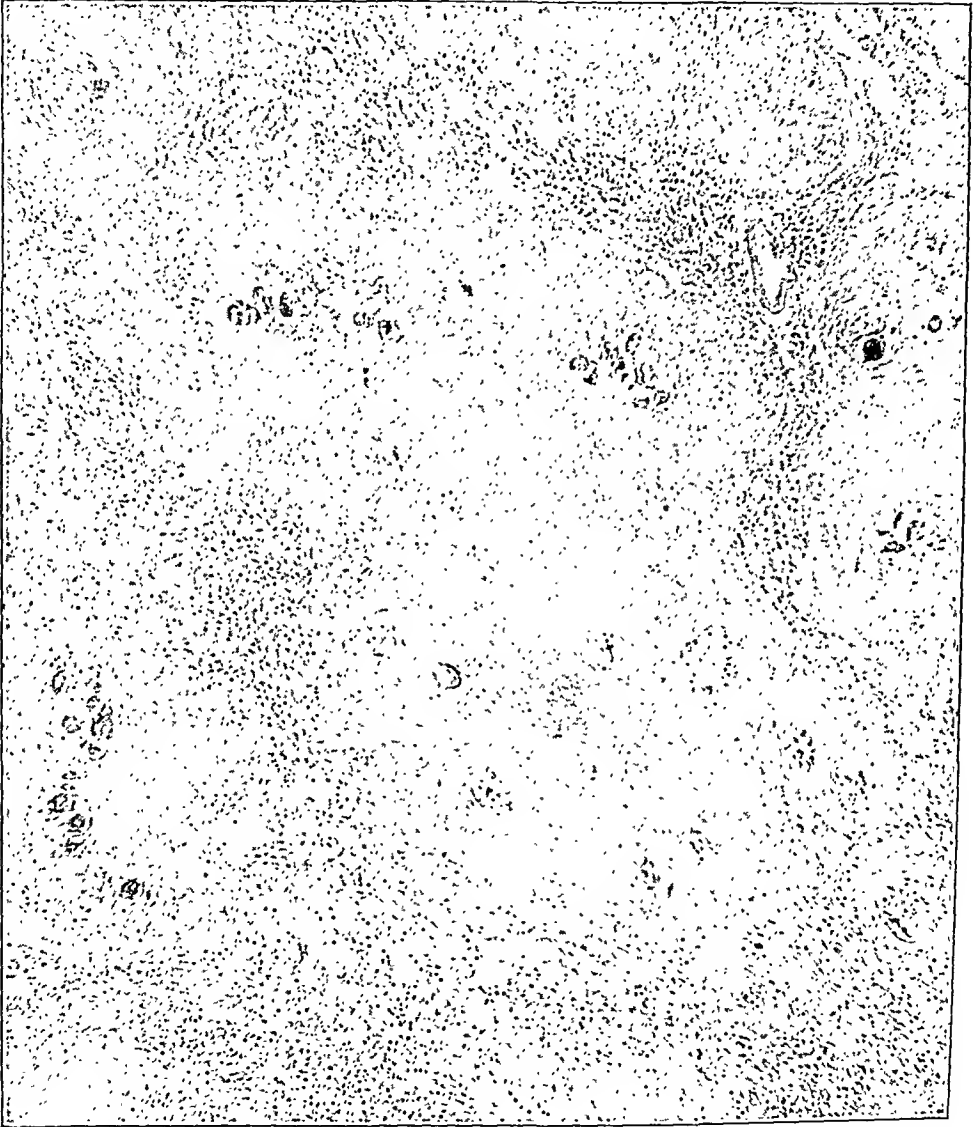


Fig. 1.—Photomicrograph ($\times 100$) showing numerous ova in the granulation tissue (United States Army Medical Museum Neg. No. 90755).

type of organism. The general appearance of the tissue was that of an extensive granuloma with large areas of caseous necrosis, around which were clusters of the cysts of the parasite. In some places these cysts appeared in large groups, while in others they occurred singly or in groups of two or three. The tissue reaction about the caseous areas was one of gliosis, with the scattered appearance of giant cells of

the Langhans type. Varying amounts of cellular infiltration, comprised of eosinophils, and less frequently of mononuclear phagocytes and plasma cells, were observed.

The ova were characterized by their doubly refractile walls and darkly stained granules, which appeared about the size of the lobe of the nucleus of a polymorphonuclear leukocyte, and by their oval shape. On some of these ova spinous

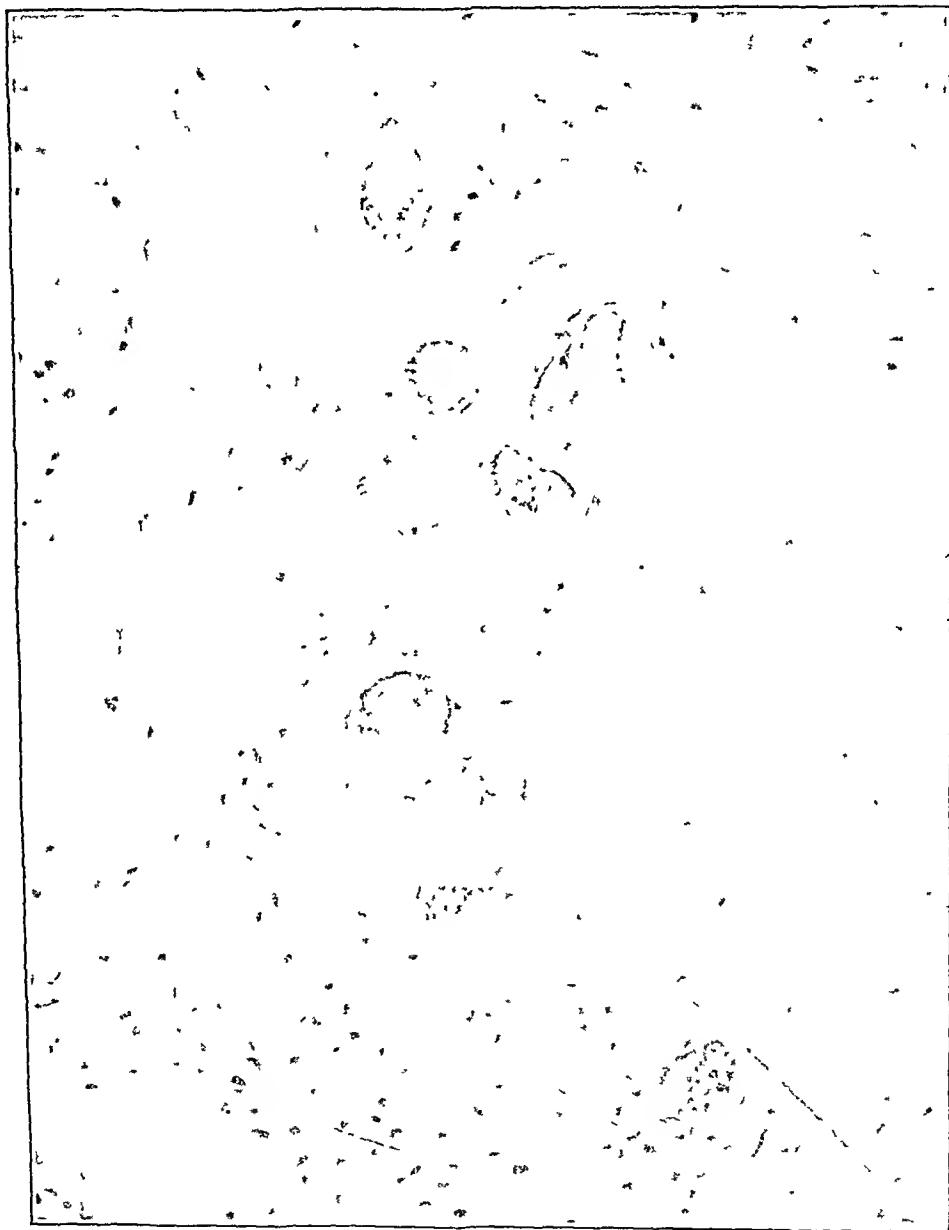


Fig. 2.—Photomicrograph ($\times 250$) showing some of the ova in granulation tissue of the removed tumor (United States Army Medical Museum Neg. No. 90756).

projections were observed on the side near one end, and rarely what appeared to be a terminal spine was seen.

A striking picture of apparent formation of miliary granulomatous areas surrounding the larger caseous areas was also noted. These granulomatous areas occurred singly and in groups as miliary and conglomerate tubercles, which usually

were composed of single or multiple parasitic cysts, epithelioid cells and glial cell proliferation. Frequently these epithelioid cells contained one or more giant cells with peripheral nuclei, and usually they were surrounded by dense glial tissue, having the appearance of a hyaline collar.

Over the surface of the tumor there was thickening of the leptomeninges, which was associated with increased vascularity and leukocytic infiltration, predominantly lymphocytic in character, with a few plasma cells and eosinophils.

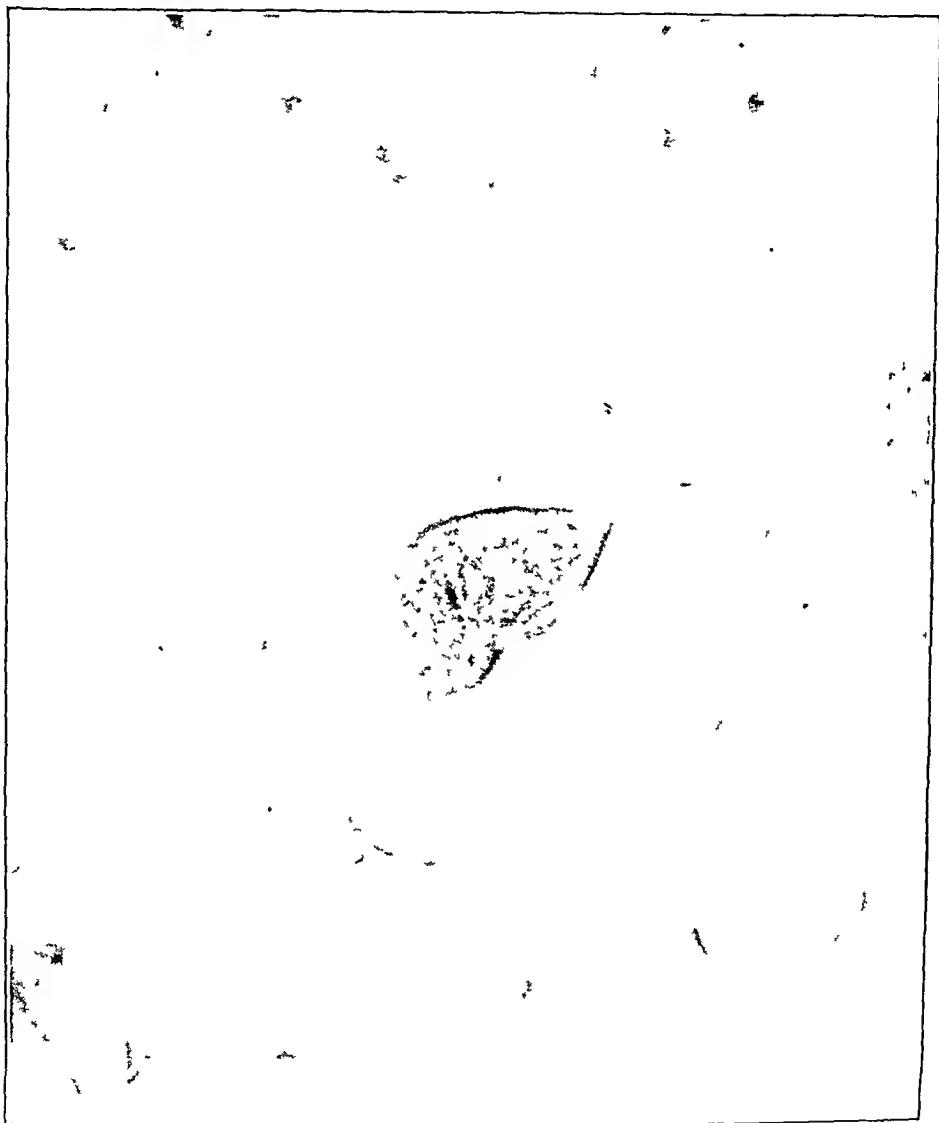


Fig. 3—Photomicrograph ($\times 480$) showing a higher power view of the ova (United States Army Medical Museum Neg. No. 90757).

The pathologic diagnosis was granuloma of the brain (schistosomiasis).

Postoperative Course.—In view of the unusual observation, the patient was interviewed again concerning a history relative to schistosomiasis. He told of being overseas at Finchaven and New Guinea for about five months, and at Hollandia, Netherlands New Guinea, for approximately four months. He was on Leyte on

Oct. 20, 1944 and remained there about one month, after which he went to Mindoro with his outfit. While on Leyte, he occasionally bathed in fresh water streams, in an area endemic for schistosomiasis japonica, and the infection was undoubtedly picked up there. Surprisingly, he gave no history of symptoms usually associated with the condition, and nothing, moreover, was found on general physical examination.

After the diagnosis had been established, the stools were examined repeatedly for ova, but none were found. Repeated urinalysis also disclosed nothing unusual. Repeated blood counts revealed a slight eosinophilia on only a few occasions, and likewise a slight leukocytosis. Anemia was never evident. The patient was placed under treatment with potassium iodide for a month, and he was also given a course of stibophen, totaling 80 cc.

Ophthalmologic examination after operation disclosed that the papilledema had receded and, again, that the peripheral fields were normal, but the enlargement of the blindspots was still evident.

Although for approximately four weeks the patient noticed no improvement in his headaches, the postoperative course was essentially uneventful. With the closure of the Hammond General Hospital, he was transferred to the Ashford General Hospital at White Sulphur Springs, W. Va., for further observation, treatment and disposition. A letter written by him there, on Jan. 25, 1946, stated that about Dec. 10, 1945 his headaches had ceased completely and that "all in all, I feel pretty good except that I get shaky once in a while."

A second letter from the patient written on April 16, 1946, told of his getting treatments with antimony potassium tartrate, the first of which left him weak and tired for a few days. No mention was made of his condition otherwise, and he wrote that he was looking forward to his discharge from the service some time prior to June.

The patient's third letter, written on June 24, 1946, is quoted as follows: "You can say that May 15 was my lucky day. I've been discharged from the Army. I haven't been doing much of anything since I left. The only work I'm doing now is around the house, and it seems that I can't do much of that. My legs seem to give out, and I have to sit down for a while. I often take little walks to get some of my strength back in my legs. I still have occasional headaches on the right side and in the back of my head. I haven't had any sort of spells for quite a while, and I hope I don't. This is about all I can say, Doctor, and I shall write again soon."

HISTORICAL REVIEW⁹

While the present paper is concerned primarily with the uncommon feature of schistosomiasis japonica affecting the central nervous system, and although a detailed consideration of the history, pathogenesis, treatment and course of schistosomiasis is available in the standard textbooks of parasitology, it seems hardly appropriate to omit entirely a discussion of these important phases of the subject.

A Japanese physician, Fujii, first mentioned the disease in 1847. The eggs of the parasite were discovered in various organs of patients in 1890 by Yamagiwa, who ascribed the etiologic role in the infection to the eggs. The eggs were first observed in the feces by Kasai in 1903. The

9. Craig, C. F., and Faust, E. C.: *Clinical Parasitology*, ed. 3, Philadelphia, Lea & Febiger, 1943, p. 385.

female worm was discovered in the portal vein by Fujinami in 1904, by Miyagawa in 1912 and by Miyairi and Suzuki in 1913.⁹

ETIOLOGIC AGENT¹⁰

In contrast to other trematodes, the adult worms of the schistosomes parasitic in man have separate sexes. Some of the eggs deposited in the small venules of the intestinal wall by the female worm are extruded and discharged into the feces, where in a few hours they are hatched, to liberate a ciliated, free-swimming larva, or miracidium. This larva invades the soft tissues of the intermediate host, an appropriate amphibious snail, in which asexual multiplication occurs and results in the production of numerous, free-swimming, fork-tailed cercariae, which are discharged only when the snails are at or below water level. Only certain species of amphibious snails are suitable for the larval development of *S. japonicum*, and sources of infection are limited to regions where these species are present. The molluscs are small and are most abundant in still water.

Infection generally is acquired by contact with water infected with cercariae. On contact with the skin of mammals which enter infected water, the cercariae cast off their tails and in the course of twenty-four hours penetrate to the cutaneous capillary beds, enter the venous circulation and are carried through the right side of the heart to the lungs; from there they filter through the pulmonary capillaries into the chambers of the left side of the heart to the systemic circulation. Only the parasites reaching the intrahepatic portal circulation via the mesenteric artery and capillaries proceed to feed, grow and migrate to the branches of the mesenteric veins. In the mesenteric venules the mature worms are paired sexually, and here egg deposition occurs. These eggs pass through the submucosa and mucosa and are extruded into the lumen of the bowel, together with extravasated blood.

Greenfield and Pritchard¹¹ considered two methods by which the ova may reach the brain. In the first, the circulating ova which pass the barrier of the liver and the lungs arrive embolically; in the second, the circulating larvae develop into adults in the veins of the brain instead of in the portal system and the ova are extruded in situ. In their cases, as in our case, the cerebral lesions were mainly in the posterior part of the parietal lobes, suggesting that the eggs were deposited by the female either in or near the place where they were observed. While in their opinion it was possible, it seemed unlikely that a very large number of eggs might be carried by the blood stream to one part of the brain, and

10. Craig and Faust.⁹ *Schistosomiasis Japonica*, Bull. U. S. Army M. Dept. 4:273, 1945.

11. Greenfield and Pritchard.⁵ Chalgren, W. S., and Baker, A. B.: *Tropical Diseases: Involvement of the Nervous System*, Arch. Path. 41:66 (Jan.) 1946.

more probable that the adult worms were lying in one of the cerebral venous sinuses. The authors noted that it would be easy for the female to pass a certain distance up the posterior anastomotic vein from the lateral sinus and to lay her eggs in the smaller venous radicles entering this vein.

COURSE AND SYMPTOMATOLOGY¹²

Because of the frequently transient character of the initial symptoms, they often pass unobserved; for this reason, a history of exposure is most important diagnostically, particularly in a group of patients with the same exposure and clinical course.

Immediately after exposure, itching and a papular rash may occur, but usually the first symptoms are manifest three to ten weeks later. These may include chills and fever, itching, unproductive cough, headache, nuchal stiffness and pain, pain in the chest or epigastrium and general abdominal discomfort or cramplike pain. Anorexia and loss of weight often are striking, but diarrhea usually is not severe. Urticaria, edema, signs suggestive of bronchopneumonia and abdominal tenderness may be present, and enlargement of the lymph nodes may be demonstrable. Uncommonly, signs of involvement of the central nervous system appear. The liver and, later, the spleen are often palpable. Roentgenograms of the lungs may reveal scattered areas of infiltration.

In the early stages, the blood picture shows a rapidly increasing white cell count with pronounced eosinophilia, without any significant anemia. After egg deposition has been initiated, the stools may contain mucus and blood as well as eggs, and this diarrhea often persists from two to ten weeks. While there may be relapses and remissions, if reinfection does not occur, spontaneous cessation of early symptoms ultimately takes place in most cases. Eventually, as the result of the reaction of the affected tissues to increasing numbers of eggs deposited in them, an extensive reparative process and proliferation of tissues take place. There may be evident thickening of the intestinal wall; and formation of papillomas, thrombosis of the mesenteric, portal or splenic veins, cirrhosis of the liver, splenomegaly and ascites may be present. Dysentery may recur from time to time, and emaciation and anemia may be severe. At such late stages eosinophilia is rarely present, and the stools seldom contain schistosome eggs.

TREATMENT¹⁰

Aside from the supportive therapeutic measures usually indicated, the early institution of chemotherapy is the only effective method, and the agents commonly employed are the compounds of antimony, stibophen

12. Faust, E. C., and Meleney, E. H.: *Studies on Schistosomiasis Japonica*, Monograph 3, Baltimore, American Journal of Hygiene, 1924, p. 339.

and antimony potassium tartrate. Trivalent antimony in the form of stibophen, also known as "fuadin" and neoantimosan, is supplied in ampules containing a 6.4 per cent solution, or about 0.064 grain (4 mg.) of stibophen per cubic centimeter. Ordinarily, the first three doses, of 1.5, 3.5 and 5.0 cc., are given on successive days, while on the subsequent alternate days, providing no toxic effect other than nausea appears, 5 cc. is given until a total of sixteen doses has been administered, or 75 cc. of the solution, containing 0.653 Gm. of antimony.

After an interval of two weeks the course of treatment is often repeated. With stibophen therapy the only commonly occurring toxic symptoms are nausea and vomiting, though rarely joint and muscle pains may be manifest. Depending on the circumstances of the toxic manifestation, the dose is usually reduced or the drug temporarily or permanently discontinued.

Antimony potassium tartrate is preferred by other authors as a more effective therapeutic agent. It is given slowly, by intravenous injection, two or three hours after a light meal, when it is best tolerated; and the patient should remain recumbent for at least an hour after treatment. The first dose is 8 cc. of the 0.5 per cent solution, or 0.04 Gm. of the tartrate, and the subsequent doses, given on alternate days, are increased by 4 cc. on each occasion, or 0.02 Gm. of the tartrate, until a dose of 28 cc., or 0.14 Gm. of tartrate, has been obtained. A total of fifteen injections, or 360 cc. of solution, containing 0.648 Gm. of antimony, is given. Reduction of subsequent doses, or temporary or permanent discontinuance of the drug, depends on the circumstances of the toxic reaction. It is advised that the injection be stopped if a toxic reaction other than coughing takes place.

The toxic effects of antimony potassium tartrate include coughing immediately on injection, which is not considered important; nausea; vomiting; stiffness of the muscles and joints; a sense of constriction of the chest; pain in the upper part of the abdomen; bradycardia; dizziness, and collapse. The course of treatment should not be repeated for at least two weeks.

Since therapy at best leaves much to be desired, the prevention of schistosomiasis is obviously the important consideration and requires avoidance of contact with fresh water infected with cercariae. Moreover, only water treated so that cercariae are killed should be used for bathing, laundry and drinking purposes.

COMMENT

Intracerebral granuloma from infection with *S. japonicum* is obviously an uncommon experience; according to the literature available, only 2 other patients have been treated neurosurgically, with removal of the granuloma and apparent clinical recovery.

The interesting case we have presented was unusual in that none of the expected symptoms suggesting the etiologic possibility was present, nor was a history of any uncovered from the patient after the diagnosis had been established. Only the history of exposure in the endemic area of Leyte and Mindoro might have given a clue, but in the absence of symptoms and signs otherwise associated with the condition, and in the presence of evidence of an intracranial expanding lesion, it is not strange that the possibility of schistosomiasis was never entertained.

The 2 cases reported by Greenfield and Pritchard⁵ were surprisingly similar to our case. The convulsive episodes in their first case occurred four years after exposure to water in an endemic area, and prior to that time the patient had been in excellent health. Except for the history of exposure, there was nothing to suggest the nature of the illness in either patient, and the diagnosis, as in our case, was made only after operation. In their cases the lesion was primarily in the posterior portion of the left parietal lobe; in our case, in the right parietal lobe.

Because of the uncommon observation of the ova of *S. japonicum* intracranially, and the similarity of the lesion to the pathologic picture caused by tuberculosis, it is not surprising that tuberculoma was thought to be the likely pathologic diagnosis until the ova were identified.

While a large granuloma was removed surgically, the probability of the infection having spread elsewhere intracranially remains. Interesting was the clinical improvement following stibophen therapy. Whether or not treatment with potassium iodide is helpful in such cases is probably debatable, but it seems a logical procedure in conjunction with administration of stibophen and was used similarly by Vitug, Cruz and Bautista⁶ in their second, unconfirmed, case, in which recovery followed such therapy.

Even had the diagnosis of schistosomiasis japonica been made preoperatively, which in the circumstances seems extremely unlikely, it is doubtful whether the usual means of therapy would have caused resolution of the large granuloma encountered, but it may be sufficient to control any remaining tissue infected with the ova.

In view of the recovery in the 2 cases reported by Greenfield and Pritchard,⁵ it is believed that a similar course of events can be anticipated in our case. It will be more important, however, to ascertain the patient's condition five or ten years after operation.

Uncommon as schistosomiasis is in this country, because of the large numbers of troops that have been stationed in the Southwest Pacific and infected areas, it is anticipated that the disease will be seen more frequently. In the case of persons with convulsive episodes who have been exposed to endemic areas, the possibility of schistosomiasis should be borne in mind.

SUMMARY AND CONCLUSIONS

An unsuspected and undiagnosed case of schistosomiasis japonica with a large granulomatous tumor in the right occipitoparietal region of the brain, removed surgically with recovery, is reported. Except for previous exposure in the endemic area of Leyte and Mindoro, the patient gave no history or clinical evidence ordinarily encountered in cases of the infection, and operation was performed for an intracranial expanding lesion.

The history, etiology, course and treatment of schistosomiasis japonica are briefly discussed.

Schistosomiasis japonica with cerebral metastases is uncommonly observed; a review of the available literature shows that our case is the third with craniotomy, removal of the intracerebral granuloma and recovery, and the first to be reported in this country. The 2 cases previously reported by Greenfield and Pritchard were strikingly similar to the present one in most respects.

Because of the large numbers of troops that have been stationed in the Southwest Pacific and endemic areas, it is believed that this infection, which has been uncommon in the United States, will be seen more frequently. In persons who have been exposed to endemic areas and have had convulsive attacks, the possibility of schistosomiasis should be borne in mind.

NOTE.—Since this paper went to press, a fourth letter from the patient, written Aug. 8, 1947, has been received. He stated:

"... As for myself, I feel a lot better than I did while at Hammond or at Ashford. Once in a while my left eye starts bothering me. The pain lasts only about three days at the most. Otherwise, I feel all right. This is about all I can say now but will write again soon."

306 East Los Olivos Street, Santa Barbara, Calif.
St. Joseph Hospital, Kansas City, Mo.

PSYCHOSIS DURING WITHDRAWAL OF MORPHINE

A. Z. PFEFFER, M.D.*
NEW YORK

THE PSYCHOSES usually attributed to the use of morphine may be classified as follows: (1) chronic psychosis due to habitual use; (2) psychosis due to withdrawal; (3) psychosis due to idiosyncrasy to the drug.

At the United States Public Health Service Hospital, Lexington, Ky., which is devoted primarily to the treatment of drug addiction, and where this study was made, there has been little experience with the last type (psychosis due to idiosyncrasy), since the patients are addicts and therefore habitually use large doses of morphine. Nevertheless, it is stated that this type of psychosis does occur.¹ It is rare, however, and appears more frequently in women. It is characterized by excitement or delirium. The findings of a previous study² indicate that the habitual use of morphine does not cause a chronic psychosis.

The present study is concerned with an evaluation of the second type, psychosis due to withdrawal of morphine. It is generally agreed that many of the psychoses observed during withdrawal of morphine are toxic psychoses consequent to the coincidental use of other drugs, such as alcohol and barbiturates, or scopolamine and atropine, in "cures."³ However, most authors concur in the opinion that in some instances a psychosis is caused by the withdrawal of morphine alone.⁴

From the United States Public Health Service Hospital, Lexington, Ky.

*Formerly Passed Assistant Surgeon (R), United States Public Health Service; now at the Psychiatric Division of Bellevue Hospital, and on the staff of the Departments of Psychiatry and Neurology, New York University College of Medicine.

1. Goodman, L., and Gilman, A.: *Pharmacological Basis of Therapeutics*, New York, The Macmillan Company, 1941. Bastedo, W. A.: *Materia Medica, Pharmacology and Therapeutics and Prescription Writing for Students and Practitioners*, ed. 3, Philadelphia, W. B. Saunders Company, 1932.

2. Pfeffer, A. Z., and Ruble, D. C.: Chronic Psychoses and Addiction to Morphine, *Arch. Neurol. & Psychiat.* 56:665-672 (Dec.) 1946.

3. Noyes, A. P.: *Modern Clinical Psychiatry*, ed. 2, Philadelphia, W. B. Saunders Company, 1939. Kronfeld, A.: Clinical Interpretation of the So-Called Abstinence Delirium of Morphine Addicts, *Jahresk. f. ärztl. Fortbild.* 24:29-38, 1933.

4. Henderson, D. K., and Gillespie, R. D.: *Textbook of Psychiatry for Students and Practitioners*, ed. 4, New York, Oxford University Press, 1936. Strecker, E. A., and Ebaugh, F. G.: *Practical Clinical Psychiatry*, ed. 5, Philadelphia, The Blakiston Company, 1940.

PRESENT INVESTIGATION

Of approximately 500 addicts from whom morphine was withdrawn, 12, or 2.4 per cent, were psychotic during the period of withdrawal. The usual procedure of withdrawal consisted in gradual reduction of the dose of morphine sulfate over a ten day period, beginning with administration of $\frac{1}{4}$ grain (16 mg.) every four hours. Three grains (0.194 Gm.) of phenobarbital was given at 11 a. m. and again at bedtime. Intravenous administration of fluids, flow baths and other supportive therapy were given when indicated. This plan was varied according to the patient's condition. As indicated in the case reports, some of the schizophrenic addicts had abrupt withdrawal of the drug, so that the intensity of the signs of abstinence could be compared with the data of Kolb and Himmelsbach⁵ for nonschizophrenic addicts from whom the drug had been withdrawn abruptly.

Each of the 12 patients was carefully examined prior to, during and after withdrawal. Six patients had a chronic psychosis long before withdrawal. Four of these had schizophrenia, and 2 had chronic alcoholic psychosis. Three of the 4 schizophrenic addicts were observed for several months prior to withdrawal of the drug, so that a clear and complete picture of their mental status prior to withdrawal was obtained. The fourth schizophrenic addict had been observed on a previous admission; in addition, he was observed for approximately two weeks

Factors in Psychoses During Withdrawal of Morphine

Psychoses prior to withdrawal.....	6
Schizophrenia	4
Alcoholic chronic hallucinosis.....	1
Alcoholic deterioration	1
Drug intoxication during withdrawal.....	4
Barbiturates	3
Delirium tremens	1
Meningoencephalitis, chronic and acute, cause unknown.....	1
Degenerative encephalopathy and barbiturates.....	1

prior to withdrawal of the drug. These 4 schizophrenic addicts were observed after withdrawal of the morphine for periods varying from a few months to a year.

Case 1, and the cases which follow, illustrate many of the aspects and observations of this study.

CASE 1.—Delirium following abrupt withdrawal of morphine from an addict with paranoid schizophrenia. H., an addict aged 46, had a psychosis diagnosed as schizophrenia at several veterans hospitals during the previous eleven years. The patient was observed for fifty days prior to withdrawal of morphine. The symptoms were those of paranoid schizophrenia. His general behavior was not bizarre. He was attentive and cooperative during interview. He displayed moderately severe anxiety. A poorly systematized delusional system revolving around persecution by the Government was elicited. There were somatic delusions in the form of electric shocks. He claimed that people in the street called him "S. O. B." and "dope fiend," and that the Devil told him, in a voice which he thought was real, to commit sins. He stated that he heard the voice of his dead sister. He was well

5. Kolb, L., and Himmelsbach, C. K.: Clinical Studies of Drug Addiction: Critical Review of Withdrawal Treatments with Method of Evaluating Abstinence Syndromes, *Am. J. Psychiat.* 94:759-799, 1938.

oriented as to time, place and person. Calculating ability and recent and remote memory were fair. The Bellevue-Wechsler subtests showed a typical pattern for schizophrenia, and the Rorschach test indicated the disease. On admission, the patient was found to be addicted to the use of unknown amounts of morphine. He was given $\frac{1}{2}$ -grain (32 mg.) of morphine sulfate every four hours for fifty days prior to withdrawal of the drug. Withdrawal was abrupt, except for two $\frac{1}{2}$ -grain (32 mg.) doses of morphine sulfate given fifty-six and seventy-six hours after withdrawal; this was done because the significant observations had already been made and the patient was uncomfortable. The observations at various intervals after the last dose of morphine are given in the following protocol:

Interval After
Last Dose

24 hr.: The patient is tremulous, yawning, flushed and restless. He has visual hallucinations of large men and hears them say, "You're going to die; we're going to cut you up." He responds to the voices and says, "No, I'm not going to die." He will not eat because he thinks the food may be poisoned. The affect is notably flattened in relation to the fearful ideas expressed. He is well oriented as to time, place and person.

Interval After
First Dose

31 hr.: The patient alternately thrashes in bed, asking for morphine, and dozes. He is disoriented as to time and place. The hallucinations are similar to those during the previous observation. The effect remains relatively flattened.

48 hr.: There are no changes in the condition previously observed.

58 hr.: Hallucinations are less vivid than before. The patient confabulates. He is oriented in all spheres.

70 hr.: The condition is unchanged except that there is no confabulation. The picture now is approximately the same as that prior to withdrawal of morphine.

96 hr.: The condition is unchanged.

8 days: Auditory hallucinations are now "friendly." They say, "Hey, Jim, are you off that stuff? Get off and stay off."

15 days: The patient claims that he has had no hallucinations for seven days. There are no further changes.

17 days: The patient has a "strong feeling" that he will not live. He states that the washbowl is charged with electricity and that it shocked him. He regards this as part of the plan of the government to persecute him. The patient's mental status does not differ from that prior to withdrawal.

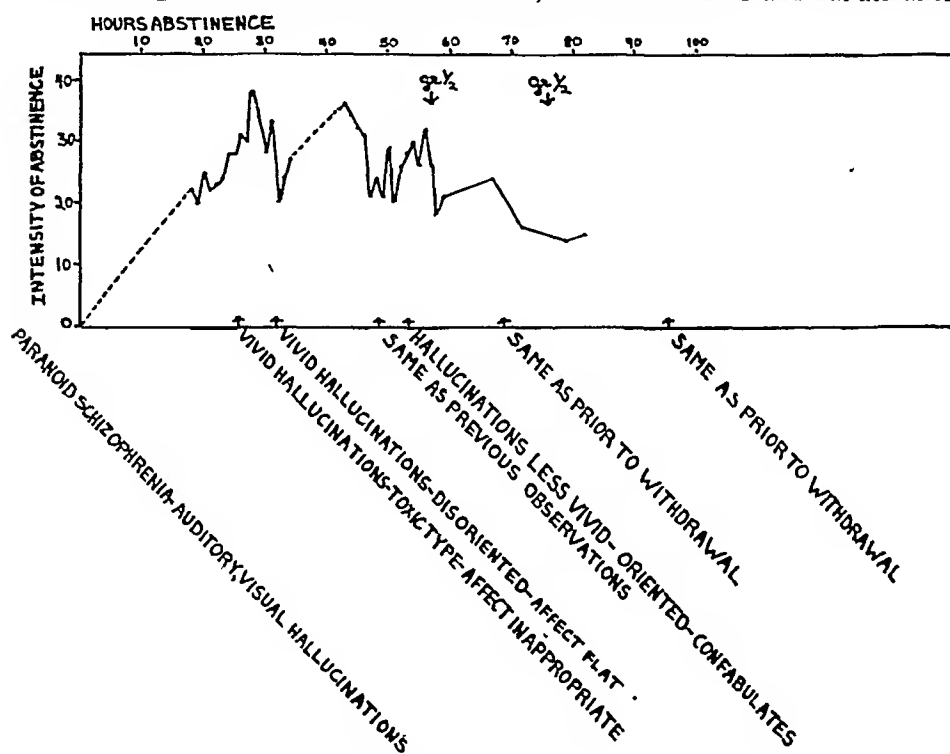
The intensity of the physical signs of withdrawal, based on yawning, lacrimation, rhinorrhea, perspiration, anorexia, goose flesh, dilated pupils, tremor, restlessness and emesis, was evaluated in accordance with the method of Kolb and Himmelsbach.⁵ These data are indicated in the graph, with the correlated psychiatric data. In this patient, the signs of withdrawal for the first fifty-six hours did not differ in intensity from those presented by the nonschizophrenic addicts observed by the authors, although the intensity was lower than the average for their group of 65 patients.

CASE 2.—Another addict with paranoid schizophrenia, with an inactive "habit," claimed that an electric current was being used on his mind and that his body had changed in shape. He heard voices call him obscene names, and he was tense and suspicious. He gave this information only after much urging, during several interviews. He was given $\frac{1}{4}$ grain (16 mg.) of morphine sulfate four times a day, and during the next two weeks this dose was increased to 2 grains (0.13 Gm.) six times a day. This dosage was continued for the next three and one-half months. It was planned to withhold morphine for the entire period of withdrawal; but because the patient had signs of cardiac decompensation at the twenty-third hour he was given $\frac{1}{4}$ grain (16 mg.) of morphine sulfate, and between the twenty-third and the eighty-first hour a total of $2\frac{1}{2}$ grains (163 mg.) was administered.

The psychiatric changes during withdrawal consisted in a freer expression of abnormal thought content, with surprisingly little increase in anxiety as compared with that to be expected during such a rigorous regimen of withdrawal.

The physical signs of withdrawal were less severe than was expected, and there was a striking absence of sweating; "goose flesh" was constantly present, persisting even during sleep; this sign is usually transient during withdrawal. Approximately one week after the beginning of withdrawal of the drug the psychiatric status was at the prewithdrawal level.

CASE 3.—The third addict with paranoid schizophrenia was delusional and hallucinatory prior to withdrawal of the drug. During withdrawal, he expressed the same thought content in a clear sensorium, but the delusions and hallucinations



Mental status correlated with intensity of signs of abstinence.

were more vivid. He became dangerously assaultive because he thought a "dirty machine" was being used on him constantly to effect sexual changes.

CASE 4.—The fourth addict had schizophrenia in partial remission. He was seclusive and preoccupied with Yogi philosophy. During withdrawal from the habitual use of a small dose of the drug there was little change in his mental status except for slight increase of anxiety. He gave a history indicative of an acute flare-up of his psychosis, with delusions of persecution and hallucinations, six years previously, during withdrawal from the habitual use of a large dose.

Thus, each of the 3 schizophrenic addicts who had withdrawal of large amounts of morphine showed increased anxiety with increased vividness in their delusions and hallucinations. One of the 3 patients became disoriented.

Summary of Remaining Cases.—A patient with chronic alcoholism who had not been drinking recently, but had experienced frequent episodes of alcoholic hallucinosis in the past twenty years, had vivid hallucinations during withdrawal of morphine, but only at night. His hallucinations were of scooters and fast-moving trains.

A patient who had had chronic alcoholism for forty years and showed changes in memory became greatly confused and disoriented during withdrawal of morphine. Several weeks after withdrawal his mental status returned to the prewithdrawal level, showing changes in memory, but no confusion or disorientation.

From 4 patients barbiturates were withdrawn, in addition to morphine. One had ingested 67 grains (4.35 Gm.) of pentobarbital sodium in the forty-eight hours prior to withdrawal. He became disoriented, had auditory and visual hallucinations of a toxic type and exhibited ataxia, nystagmus and dysarthria. All signs of toxicity, including the psychosis, disappeared ten days after abrupt withdrawal of barbiturates and rapid reduction of morphine over a ten day period.

Another patient, who had used 25 grains (1.63 Gm.) of seconal sodium daily for one year, presented the same symptoms as the previous patient except for the absence of nystagmus, ataxia and dysarthria. The psychosis cleared two weeks after the abrupt withdrawal of barbiturates and the rapid reduction of morphine.

In addition to morphine, 1 addict had used 12 to 18 grains (0.78 to 1.17 Gm.) of sodium amytal daily for a year. On the last night of a ten day period of reduction of the morphine he was delusional and hallucinated. He both heard and saw the devil; he saw elephants and tigers. He said that everyone was talking about him. He feared that he would die. At the time of examination he was well oriented. He was given $\frac{1}{4}$ grain of morphine sulfate six times a day and additional symptomatic treatment, with immediate decrease of anxiety; but hallucinations did not cease for ten days. In five weeks, during which time morphine was gradually withdrawn, the psychosis cleared entirely. The picture then presented was that of a severe neurasthenic psychoneurosis.

A patient with chronic alcoholism who had used morphine for two years and $\frac{1}{50}$ grain (1.3 mg.) of scopolamine hydrobromide daily for eight months, and who had been drinking heavily just prior to withdrawal of the drugs, became restless, tremulous and disoriented. He had hallucinations of monkeys climbing over him and the ringing of bells. The entire picture was similar to that of delirium tremens. According to the patient, even prior to the use of morphine and scopolamine he had had similar episodes after heavy drinking.

A patient with an organic type of psychosis died during withdrawal of the drug, and postmortem examination revealed acute and chronic meningoencephalitis of undetermined cause. An addict with degenerative encephalopathy, probably of vascular origin, which was demonstrated by air encephalography, became confused and disoriented during withdrawal of the drug. Prior to and after withdrawal he had changes in memory and poor calculating ability, but orientation was good.

COMMENT

While it appears that withdrawal of morphine is not sufficient in itself to cause a psychosis, it is apparent that it may intensify the symptoms of a psychosis that already exists; this was demonstrated by the patients who had a psychosis prior to withdrawal. It is interesting that in the case of a schizophrenic addict who had withdrawal of

morphine alone, the increased vividness of the delusions and hallucinations together with the disorientation, resulted in the picture of a toxic psychosis.

It is of course impossible to know how much the withdrawal of morphine contributed to the picture of the toxic psychosis apparently produced by alcoholism and barbiturates; there is little doubt that at least anxiety was increased.

In view of the fact that so large a percentage of persons with addiction to morphine have severe neurotic traits, it is curious that more do not become psychotic during withdrawal of the drug. The withdrawal of morphine, even with the best medical care, is a rigorous, anxiety-producing experience. These facts perhaps lend support to the thesis that the psychoneuroses and the psychoses are not a continuum, but, rather, are distinct entities. The development of delirium in the first schizophrenic addict suggests a close relation between schizophrenia and toxic psychosis.

The findings in this study indicate that withdrawal of morphine, of itself, is rarely, if ever, a cause of psychosis. In each instance complicating factors (schizophrenia and various types of organic psychoses) accounted for the psychosis during withdrawal. It must be noted that rapid withdrawal (ten days) is the method usually employed and that with quicker withdrawal more instances of psychoses would perhaps have occurred. Yet Himmelsbach and Williams⁶ found, during the abrupt withdrawal of morphine from 400 addicts under close supervision so that no other drugs could be used, only 1 patient who became obviously psychotic.

Bellevue Hospital, Psychiatric Division.

6. Himmelsbach, C. K., and Williams, E. S.: Personal communication to the author.

Abstracts from Current Literature

Physiology and Biochemistry

EFFECT OF COMPOUNDS RELATED TO GLYCOLYSIS IN MUSCLE ON THE SENSITIVITY OF MUSCLE TO ACETYLCHOLINE AND POTASSIUM. CLARA TORDA and HAROLD G. WOLFF, *Am. J. Physiol.* **145**:419 (Jan.) 1946.

Torda and Wolff studied the effect of products of glycolysis, substances involved in the esterification of carbohydrates and substances inhibiting glycolysis. The effects were studied on the rectus abdominis muscle of frogs and on the acetylcholine and potassium sensitivity of this muscle. Shortening of the muscle was produced by hexose diphosphate, adenosine triphosphate, fluoride citrate and oxalate. Acetylcholine sensitivity of the muscle was increased by hexose diphosphate, pyruvic acid, acetone, acetaldehyde, adenosine triphosphate, creatine phosphate, creatinine, inosinic acid, epinephrine, physostigmine and fluoride. Acetylcholine sensitivity was not altered by dihydroxyacetone monophosphate, β -glycerophosphate, acetylphosphate, propionic acid, acetic acid, acetoacetate, ethyl alcohol, creatine, ammonia, citrate, oxalate, phosphate, pyrophosphate glyceraldehyde or monoiodoacetate. Acetylcholine sensitivity was decreased by high concentrations of butyric acid and by β -hydroxybutyric acid. Potassium sensitivity of the muscle was decreased by Ringer's solution with high calcium content and by potassium-free Ringer's solution, epinephrine, acetaldehyde, and β -hydroxybutyric acid. Potassium sensitivity was not altered by propionic acid, acetone, ethyl alcohol, creatine phosphate, glyceraldehyde or monoiodoacetate. Torda and Wolff could find no direct relation between -SH groups and changes in acetylcholine and potassium sensitivity of muscle. The authors conclude that lowering of the calcium ion content of muscle increases potassium sensitivity and induces shortening of the muscle, and that changes in intracellular adenosine triphosphate increase acetylcholine sensitivity.

FORSTER, Philadelphia.

THE INFLUENCE OF AVOIDANCE CONDITIONING OF THE COURSE OF NON-AVOIDANCE CONDITIONING IN DOGS. G. B. WHATMORE, E. A. MORGAN and N. KLEITMAN, *Am. J. Physiol.* **145**:432 (Jan.) 1946.

Whatmore, Morgan and Kleitman found that, while the avoidance and the nonavoidance type of conditioning procedure can be used separately to develop and maintain conditioning of leg flexion performance in dogs at a high level, if the two types of conditioning are used concurrently in the same animal the avoidance conditioning has a strong deleterious effect on the course of the nonavoidance conditioning but is itself fully retained.

FORSTER, Philadelphia.

THE PERIPHERAL VISUAL ACUITY OF 100 SUBJECTS UNDER SCOTOPIC CONDITIONS. FRANK N. LOW, *Am. J. Physiol.* **146**:21 (April) 1946.

Low studied the simple visual acuity for form of 100 subjects under scotopic conditions. Fourteen points on the retinal periphery were studied. Simple form acuity under scotopic conditions is somewhat weaker than is photopic acuity in the same retinal areas. Acuity isopters for night vision are nearly circular, being flattened only on the top. This is in sharp contrast with the irregular oval isopters known for day vision. The dispersion of scores is less in scotopic than in photopic acuity. Impairment of the scotopic mechanism can prevent successful measurement with this technic. Low found that the technic under scotopic conditions is less reliable than the same technic under photopic conditions.

FORSTER, Philadelphia.

EFFECT OF EXTIRPATION OF PARASTRIATE CORTEX ON LEARNED VISUAL DISCRIMINATIONS IN MONKEYS. HARLOW W. ADES, J. Neuropath. & Exper. Neurol. 5:60 (Jan.) 1946.

Three monkeys were trained to discriminate between pairs of visual stimuli which varied with respect to size, shape and color. It was observed that monkeys so trained lose the power of this type of discrimination if areas 18 and 19 are destroyed bilaterally in one stage. The discrimination can then be relearned postoperatively at approximately the same rate as originally. If the cortical destruction is carried out in two stages with an interval between during which testing is continued, the discriminatory ability is lost. GUTTMAN, Philadelphia.

THE PYRAMIDAL TRACT: THE REPRESENTATION OF THE LATERAL CORTICOSPINAL COMPONENT IN THE SPINAL CORD OF THE CAT. A. M. LASSEK, J. Neuropath. & Exper. Neurol. 5:72 (Jan.) 1946.

Utilizing a silver stain, Lassek reports on the number of pyramidal fibers descending into the spinal cord of the cat.

Massive cortical lesions on the left side were made in a series of 8 neurologically mature cats so that the cells of origin of the pyramidal tract were completely, or almost completely, ablated. The animals were then killed at intervals of three, six, twenty-six, sixty-eight, one hundred and sixty-eight, one hundred and eighty, two hundred and fifty-four and two hundred and seventy-four days after operation. In the last 2 animals, a second, similar, operation was performed on the opposite hemisphere about thirty days preceding the date of killing. The bilaterally decorticated animals gave an opportunity to compare the effects of acute and chronic lesions, to study any possible displacement of nonpyramidal fibers into the pyramidal area and to determine the status, to some extent, of the homolateral tract.

Representative sections from the mesencephalon, pons, medulla and four regions of the spinal cord were stained either with the protein silver or the Bodian technic, mostly with the former. At all levels, the degenerated portion of the pyramidal tract on the side of the unilateral lesions was compared with the pyramidal tract in the normal, unaffected, half. Both silver methods are suitable for tracing degenerated axons, but the protein silver technic was found to be preferable in the author's hands. In the more acute stages, analysis is largely subtractive. As the glial tissue proliferates, the degenerated area becomes darker and can be more easily followed. Lassek observed that few, if any, fibers of the crossed pyramidal tract extend the entire length of the spinal cord in the cat. The tract terminates largely in the upper two thirds of the spinal cord. There is evidence that many of its fibers terminate high in the cervical region of the cord. Many fibers are normally present in the pyramidal area of the cord which do not belong to any part of the pyramidal system, including the so-called homolateral corticospinal component. Degeneration of axons of the pyramidal tract in the cat was detected as early as three days with the protein silver method of staining. Cellular activity of the supporting elements continues for nine months or more in the pyramids after massive cortical ablation. In its phylogenetic development the pyramidal tract in the cat appears to occupy a position intermediate between the lower mammals and man.

GUTTMAN, Philadelphia.

A NOTE ON A MECHANISM OF ARTERIAL RUPTURE IN CEREBRAL ARTERIOSCLEROSIS. WILLIAM J. TURNER, J. Neuropath. & Exper. Neurol. 5:168 (April) 1946.

The breaking of an inelastic substance subjected to repeated flexion may account for cerebral vascular aneurysm and rupture with cerebral arteriosclerosis, particularly when complicated by hypertension. A mechanism of this sort has not hitherto been considered.

It is well known that in arteriosclerosis the arteries become longer and more tortuous, as well as more inelastic; also, with each pulsation the arteries tend to straighten but are unable to do so because they are fixed at their points of bifurcation. It seemed possible that the combination of these factors might result in a tendency of the arterial wall to rupture near a point of bifurcation of the artery and that this tendency might be aggravated by an elevation of blood pressure.

A simple ingenious mechanical setup is described in detail. This arrangement allows for a sudden dilation of the longer of two rubber tubes. By careful regulation of the pressure, dilatation can be repeatedly developed, with eventual formation of a lax and dilated wall of the tubing prior to its final rupture. If the pressure is too greatly elevated or is maintained too long at a high level, the rupture occurs suddenly and without warning. A number of variants of the model described yielded results in accord with the foregoing statement. The more tortuous the course of the rubber tube, almost regardless of its length, the earlier will the rupture occur, and the more certainly at the distal point of fixation. In more than forty experiments the straight tube did not once rupture.

GUTTMAN, Philadelphia.

EFFECT ON THE ELECTROENCEPHALOGRAM OF LOCALIZED PRESSURE ON THE BRAIN.

MARK ALBERT GLASER and HENDRIKUS SJAARDEMA, *J. Neurophysiol.* **9:63** (March) 1946.

Glaser and Sjaardema describe a method for producing localized increased intracranial pressure. The apparatus consists of a lucite rod 0.713 cm. in diameter attached to a micrometer screw. Introduction of the lucite rod through the trephined skull produced increased intracranial pressure. The electrical activity of the cortex was recorded before, during and after the introduction of increased intracranial pressure. Glaser and Sjaardema found that slowly increasing the intracranial pressure produced alterations in the electroencephalographic pattern. These alterations included a high incidence of activity analogous to that seen in clinical and experimental epilepsy.

FORSTER, Philadelphia.

EYE MOVEMENTS FOLLOWING STRYCHNINIZATION OF THE SUPERIOR COLLICULUS OF CATS. JULIA T. APTER, *J. Neurophysiol.* **9:73** (March) 1946.

Apter found that strychninization of a small area of the superior colliculus of the cat activated the path of reflex attraction of the eyes toward a light in the peripheral visual field. Each point on the superior colliculus was found to regulate movement of the eyes to a particular part of the visual field, thus, medial points caused upward and lateral movements, while lateral points caused lateral downward movements. Each colliculus was concerned with movements to the contralateral visual fields. Conjugate movements of the eyes were found to be due to contraction of agonist and relaxation of antagonist muscles, and this regulation was mediated by the superior colliculus. Charting of the superior colliculus for control of localized ocular movements correlated for projection of the visual field on the colliculus.

FORSTER, Philadelphia.

SPINAL CONDITIONING IN DOGS. W. N. KELLOGG, N. H. PRONKO and JAMES DEESE, *Science* **103:49** (Jan. 11) 1946.

There is evidence in the literature that learning—or what appears to be learning of a rudimentary sort—can occur in the caudal extremities of higher vertebrates after the spinal cord has been completely transected. These observations were originally made on acute spinal dogs. If these observations could be confirmed and elaborated on, it would seem that the organism, or a fragmentary part of it, can form simple associations without the aid of the cerebrum or any of the higher centers of the central nervous system and that these centers are, therefore, unneces-

sary for the occurrence of learning of the sort indicated. The authors attempted conditioned reflex training with chronic spinal dogs.

The conditioned stimulus in the present experiments was an electric shock to the left rear foot, and the unconditioned stimulus was a shock to the right rear foot. The response to be conditioned was the moving or flexing of the entire right hindlimb. Each of the subjects was given 1,000 conditioning trials in groups of 100 trials each, spaced on alternate days over a period of about three weeks. Despite the differences in experimental technic in the two investigations, there was clear evidence in both the acute and the chronic preparations that a muscle twitch or an instantaneous jerk of the right rear leg could be evoked by the conditioned stimulus to the left rear foot. The twitch response was small in amplitude and of very short latency. The twitching movement of the right rear member may be the same as the spinal conditioned response observed in the acute preparation by Shurrager and Culler.

The twitch response observed in the chronic spinal animals, however, was only a part of the behavior elicited by the conditioned stimulus. Records of movement of the right hindlimb also disclosed a second, and conflicting, type of reaction. In place of the muscle twitch or incipient flexion, there often occurred an extension of the right rear limb, i. e., the crossed extension reflex. Although the extension response was initiated immediately by the conditioned shock, it usually lasted from two to three seconds. With respect to duration it had no resemblance, therefore, to the very brief jerk of the flexing muscles.

The two sorts of reflex movements were antagonistic and mutually inhibitory. They never occurred together on the same trial. One response usually predominated for several trials and was then superseded by the other. Yet there can be no doubt that both responses were genuine and that they were unstable, appearing and disappearing, even though the stimulating conditions remained the same.

Frequency graphs of the flexing twitch, as well as of the extension response, were so irregular that they were quite unrecognizable as learning curves. The only similarity to the typical curve of learning was that each response was absent at the start of training and increased somewhat in frequency during the later trials. When both the crossed extension and the flexion reaction were considered together, the combined frequency of responsiveness for all animals rose gradually for the first three hundred trials and continued at approximately 20 per cent for the remaining 700 trials.

In spite of this irregular level of about 20 per cent, which persisted when the frequencies of the two responses for all subjects were pooled, no evidence of retention was observed over the intervals between experimental sessions in the behavior of any one dog considered by itself. The spinal behavior of the present subjects cannot satisfactorily be fitted into the conditioning formula, since that behavior was a combination of two antagonistic responses, now one occurring, now the other.

GUTTMAN, Philadelphia.

THE EPIDEMIOLOGY OF THE 1945 OUTBREAK OF POLIOMYELITIS IN MAURITIUS. ALLAN M. MCFARLAN, *Proc. Roy. Soc. Med.* 39:323 (April) 1946.

In February 1945, in Mauritius, after a cyclone which caused widespread damage to dwellings, there occurred intestinal diseases in increasing prevalence and an epidemic of poliomyelitis. During the first five months of 1945 there were at least 1,018 cases of the disease, with a rate of attack of 2.4 per 1,000 of population. Of 851 cases in one series, 64 per cent were of children under the age of 5 years and 95 per cent of children under the age of 10 years. No definite paralysis was present in 4 per cent of the cases, whereas in 86 per cent the legs were affected. A symmetric, somewhat steep curve, resembling that of an influenza epidemic, characterized the weekly incidence of cases and suggested an infection with a very short incubation period and a high degree of infectivity, unlike typical paralytic

poliomyelitis. Such a curve might apply to a carrier epidemic of the virus. Because casual contact apparently sufficed to transmit infection, the author concludes that the presence of the virus in the pharynx may be more important for the spread of infection than its presence in the feces.

The outbreak, first localized in one area, spread rapidly throughout the island, apparently in a number of instances carried by healthy adult men. Except for one village, where contamination of ice cream possibly played a part in the spread of the disease, the type of epidemic suggested a spread by transient carriers. Contact was the most important factor determining infection.

BERRY, Philadelphia.

EFFECT OF PENICILLIN ON REGENERATION OF NERVES: PRELIMINARY NOTE.
O. AIDAR and C. MIGNONE, *Arq. de neuro-psiquiat.* 3:246 (Sept.) 1945.

The tibial nerve was sectioned in 32 rabbits. In 16 rabbits the site of the experimental lesion was contaminated with *Staphylococcus aureus*. In the other 16 no such organisms were introduced. Each group of 16 rabbits was then divided into two subgroups of 8 each. One cubic centimeter of penicillin (200 to 250 Oxford units) was placed at the operative site. The penicillin had no effect on the regeneration of nerves whether infection was present or not.

N. SAVITSKY, New York.

Neuropathology

NEUROPATHOLOGIC STUDY OF ACUTE HUMAN POLIOMYELITIS, WITH SPECIAL REFERENCE TO INITIAL LESION AND TO VARIOUS POTENTIAL PORTALS OF ENTRY.
H. K. FABER and ROSALIE J. SILVERBERG, *J. Exper. Med.* 83:329 (April) 1946.

Faber and Silverberg examined the tissue of the peripheral and central nervous systems of 8 patients who died of acute poliomyelitis. On the basis of concurrent lesions in the primary and secondary centers, the involvement of the various systems was found to be (a) very frequent for the trigeminal afferent system (fifth cranial nerve), (b) fairly common for the visceral afferent system (ninth and tenth cranial nerves) but less than for the fifth, (c) occasional for the gustatory system (seventh, ninth and tenth cranial nerves), (d) occasional for the upper levels of the sympathetic system (pharynx, bronchial tree, upper part of the esophagus) and (e) occasional or doubtful for the lower sympathetic system (intestine). The probability of their having acted as primary pathways for entering infection was in direct correspondence with the frequency of involvement. The vagal efferent (parasympathetic) system (tenth cranial nerve) and olfactory (first cranial nerve) system were not involved. The evidence of penetration through the upper alimentary and respiratory tracts was more conspicuous and consistent than that of penetration through the lower alimentary tract. The pharynx appears to be an especially favorable site for the primary penetration of virus into the body.

J. A. M. A.

THE PATHOLOGY OF INJURY TO NERVE INDUCED BY COLD. D. DENNY-BROWN, RAYMOND D. ADAMS, CHARLES BRENNER and MARGARET M. DOHERTY, *J. Neuropath. & Exper. Neurol.* 4:305 (Oct.) 1945.

The authors record the results of two series of experiments, both of which were carried out on cats. In the first series, the sciatic nerve was exposed aseptically and a length of 1 cm. packed off and frozen solid by a spray of carbon dioxide. After a variable interval of time the frozen part of the nerve was then thawed by the application of cool or tepid isotonic solution of sodium chloride. On the day after the operation and thereafter the animals were examined to determine the degree of motor and sensory paralysis. Weakness or paralysis of the dorsiflexors

and plantar flexors of the foot and spreading of the toes could be detected by watching the animal walk and by testing the placing reaction. Loss of touch and pain sensations could be judged by response to contact and pinching of the paw. When the animals were killed, motor responses to faradic current applied above and below the lesion were noted. The nerves were stained by a variety of histologic methods, chiefly stains for myelin (Spielmeyer), fat (oil red O) and axis-cylinders (Gros-Bielschowsky) and general tissue stains.

In the second series, cooled brine at a constant temperature, ranging from -4.0 to $+3.0$ C. in the various experiments, was circulated through a small cylindrical metal jacket surrounding a segment of sciatic nerve (20 mm.) for a measured period of time (usually two hours). The temperature of the brine was measured by thermometer at the inflow and the outflow and the temperature of the interior of the nerve by a fine thermocouple (copper-constantan) inserted between the fasciculi of the nerve. The vessels supplying the nerve were always left intact, and the entire procedure was carried out aseptically. Care was also taken to avoid kinking of the nerve. As in the first series, the animals were killed after varying periods of survival and observation and the nerves examined microscopically after suitable fixation and staining.

In addition, a few experiments were carried out in which the shaved, oiled ear of an anesthetized rabbit was transilluminated and observed in a transparent glass chamber containing circulating, cooled brine (-1.0 to -4.0 C.). However, after immersion of the ear for one hour at -4 C. there was no resultant loss of sensitivity to pinch, and since vessels of capillary size could not be satisfactorily observed these experiments were abandoned.

The observations indicate that myelin and axis-cylinders of mammalian peripheral nerve are selectively damaged by exposure to cold, the largest fibers being the most sensitive and the smallest the least sensitive. Damage to large motor fibers and nerves conveying sense of contact is caused by exposures to such temperatures as $+8.0$ C. for intervals as short as thirty minutes. The mildest degree of damage resembles that produced by transient ischemia, but the complete lesion results in the complete destruction of the myelin of the affected fibers without necessarily damaging that of smaller fibers. The demyelinated segment of the axon-cylinder degenerates. The affected myelin undergoes dissolution, and necrosis of whole nerve bundles occurs only after freezing. Regeneration is rapid and complete in all grades of the injury short of complete necrosis.

GUTTMAN, Philadelphia.

ACUTE MYELITIS: A CLINICAL-PATHOLOGIC STUDY. GEORGE B. HASSIN and SAMUEL B. BRODER, *J. Neuropath. & Exper. Neurol.* 5:106 (April) 1946.

Hassin and Broder report the case of a middle-aged man, in apparent good health, who shortly after an infection of the upper respiratory tract experienced paraparesis of the lower extremities, from which he improved and was able to resume his work. About six weeks later paraplegia suddenly set in, associated with complete anesthesia up to the level of the eighth thoracic segment and loss of deep, superficial and sphincteric reflexes. No spinal block could be demonstrated. The spinal fluid was turbid and contained 60 mg. of total protein per hundred cubic centimeters. In spite of the repeated clinical and laboratory studies, a definite diagnosis could not be arrived at, even after a laminectomy had been performed.

Postmortem examination, done about twelve hours after death, revealed that the spinal cord was covered at the lower dorsal level with a slightly gray exudate. The blood vessels in the middorsal region of the cord were dilated and in some places appeared thrombosed.

The pathologic diagnosis may be summed up as inflammation, degeneration, necrosis, meningitis and radiculitis, all confined to the spinal cord. Though diffuse, the changes were especially pronounced in the thoracic region and, as a rule, involved the white substance more than the gray, where circumscribed foci of softening were also present, with the complete preservation, however, of the

ganglion cells and the blood vessels. These showed only infiltrations, either with hematogenous elements or with compound granular corpuscles (gitter cells).

Hassin and Broder state that acute myelitis should be considered among the commonest causes of acute paraplegia. In acute myelitis both the gray and the white substance of the spinal cord are affected by an inflammatory process. These changes may be immense or be replaced by the process of softening or necrosis, with which they may be combined. The phenomena of inflammation, softening and necrosis, as observed in cases of acute myelitis, are to be considered mere gradations of one toxic-infectious disease process. The rest of the central nervous system, the brain, for instance, reacts by exhibiting proliferative vascular changes, which are those of productive encephalitis. GUTTMAN, Philadelphia.

THE CEREBRAL CORTEX IN THE VERY OLD HUMAN BRAIN. W. RIESE, *J. Neuro-path. & Exper. Neurol.* 5:160 (April) 1946.

This study of the chronologically very old brain was undertaken in order to answer the following question: Are the changes to be seen in the very old brain commensurate with the age of the patient or the length of the clinical course? Rothschild stated a few years ago that he observed no parallelism between the severity of the parenchymatous changes in the brain and the age of the patient. To date, no attention has been paid to the question of the length of the clinical course.

The material was obtained from 18 patients, aged from 77 to 107 years. All were inmates of a state hospital, and all but 5 had had senile dementia of eleven months' to fourteen years' duration. For 4 patients the diagnosis of "psychosis with cerebral arteriosclerosis" was made; the fifth, a 90 year old woman, who was admitted at the age of 55 to the state hospital with the diagnosis of "involutional melancholia," had never exhibited the senile type of psychosis. In some instances the exact onset of the disease could not be determined; in others a more or less sudden deterioration took place after a slow initial onset. The microscopic studies were made on sections prepared by the Nissl method.

It was observed that the overwhelming majority of very old brains showed at least some cortical atrophy, diffuse or regional in distribution. The degree of cortical atrophy was not necessarily proportionate to the age of the patient. The cytoarchitecture was surprisingly well preserved in the very old brains, the three types of pyramidization, granularization and spindlization being as obvious in these brains as in the brains of young and adult persons. Cellular changes were consistently present in the very old brains, but these were not proportionate to the age of the patient. Neither the degree of cortical atrophy nor the extent of cellular destruction was proportionate to the duration of the clinical history.

GUTTMAN, Philadelphia.

BILATERALLY SYMMETRIC SYMPATHICOBlastoma. MOSTO, RODAS and DANTE, *Prensa med. argent.* 33:277 (Feb.) 1946.

Bilaterally symmetric tumors were observed in the region of the adrenal glands in a man aged 52. He had complained of severe pain in the lumbar region with radiation anteriorly for about six months. There had been considerable loss in weight during this period. An abdominal tumor was palpated. There was roentgenographic evidence of a tumor in the upper and anterior part of the mediastinum. Perirenal insufflation of air was not done. An exploratory abdominal operation revealed the tumors to be of about the same size, 15 by 20 by 12 cm. The kidneys were adherent to the tumors. There were metastases to the lungs and mediastinum. Histologic examination indicated that the tumor arose from the cells of the sympathetic nervous system.

N. SAVITSKY, New York.

CEREBRAL METASTASIS COMPLICATING PRIMARY CANCER OF THE LUNG. I. M. HERNANDEZ and LOUIS IRIGOYEN, Publ. d. Centro de invest. fisiol. 9:77 (June) 1945.

Four cases of cerebral metastases were found in 50 cases of primary tumor of the lung (8 per cent). In 3 cases the metastases to the brain were multiple. At times the cerebral changes resulting from the metastases dominated the picture. In all the cases pulmonary symptoms were present before cerebral complications appeared. The authors believe that metastases to the brain take place through the blood stream directly into the lesser circulation, most frequently into the middle cerebral artery. In 1 case there were multiple metastases to the cerebrum and the cerebellum.

N. SAVITSKY, New York.

Meninges and Blood Vessels

MENINGITIS AND ABSCESS OF THE BRAIN DUE TO PANSINUSITIS. LAWRENCE T. CACIOPPO, Arch. Otolaryng. 42:47 (July) 1945.

The use of drugs, especially penicillin, has considerably improved the outlook for patients having infections of the paranasal sinuses complicated by intracranial extension. There are occasions, however, when these drugs may greatly improve the clinical picture and at the same time mask the signs of extension of the pathologic process.

Cacioppo reports the case of a man aged 33, known to have diabetes, who was admitted to the hospital complaining of headache in the left frontal region of ten days' duration. There were edema and tenderness over the left side of the forehead. The patient had chronic sinusitis with involvement of the antrum and a fistula draining into the left upper premolar region. Further examination corroborated a diagnosis of acute pansinusitis of the left side and diabetes mellitus. Sulfadiazine therapy was begun at once, and insulin was ordered. Some improvement was noted the next day, although there was definite drainage from the left frontal region. On the fourth day after his admission to the hospital, a Killian operation was done and a drainage tube inserted into the left frontal sinus. Two days after this operation meningitis developed. The cell count of the spinal fluid was 11,000 per cubic millimeter, and Babinski and Kernig signs and nuchal rigidity were present. Penicillin therapy was started, and by the eighth day the temperature had dropped from 104 to 99 F. On this day bilateral bronchopneumonia was found, though the general picture of meningitis seemed improved. On the twelfth day the patient showed signs of irritation of the left frontal lobe. The bronchopneumonia showed complete resolution; there was improvement in the meningitis, the spinal fluid cell count and the neurologic signs after a month of hospitalization, though a roentgenogram showed osteomyelitis of the frontal bone. By the end of the fifth week the patient had vomiting, headache, weakness of the right upper and lower extremities and paralysis of the right side of the face. An intracranial exploration was done, but the patient became comatose and died forty-eight hours later. Autopsy showed an acute abscess of the brain in the occipital lobe and a subdural abscess in the frontal region. Since there was no apparent communication between the two abscesses, extension was probably by way of the subdural space from the subdural abscess to the occipital lobe and thence forward. Uncontrolled diabetes added complications in this case.

RYAN, Philadelphia.

Diseases of the Brain

FIBROSARCOMA OF THE SPHENOID BONE, PRODUCING THE SYNDROME OF THE LATERAL WALL OF THE CAVERNOUS SINUS. MAX GOLDMAN and RAYMOND D. ADAMS, J. Neuropath. & Exper. Neurol. 5:155 (April) 1946.

Fibrosarcoma of the cranium is rare. Goldman and Adams report this case because of the infrequency and unusual character of the clinical syndrome produced by encroachment on the cavernous sinus.

In this case, that of a middle-aged white man, the neurologic status was complicated by jaundice, fever and chills, which were attributed to dysfunction of the gallbladder. In the middle of June the patient experienced diplopia and discomfort in the right frontotemporal region. There were ptosis of the right eyelid and paresis of the right superior rectus muscle. Within five days the paresis progressed to complete ophthalmoplegia, and on the sixth day the pupil had become dilated and fixed to light and in convergence. The corneal reflexes remained active; there was no sensory impairment over the face, and proptosis could not be detected by inspection. The optic fundi, visual acuity and visual fields were normal. Olfactory function was preserved. No other neurologic abnormalities were observed. The heart and lungs were normal. No abdominal masses or viscera were palpable. The lymph nodes were not enlarged. Roentgenograms of the base of the skull revealed no bony defects. Roentgenograms of other bones, similarly, showed no abnormality. The blood counts and studies of the cerebrospinal fluid all gave results within the limits of normal. The blood phosphatase level and the sedimentation rates were not increased.

A month later the discomfort in the forehead became intense and almost constant. About two months after onset of the neurologic symptoms and signs, examination revealed no change in his status. The patient became confused and comatose and died.

Postmortem examination revealed a mass of grayish red tissue presenting just lateral to the sella turcica on the right side. This tissue was attached to the outer surface of the dura mater and bulged into the anteromedial part of the middle fossa, and in so doing it displaced the cavernous sinus laterally. Coronal sections of the sphenoid bone revealed the full extent of the tumor. The body of the sphenoid bone was largely replaced by tumor tissue, which had extended into and filled the sphenoid sinus. The right cavernous sinus was obliterated by the lateral extension of the tumor. In cross section, the third, fourth, ophthalmic fifth and sixth cranial nerves on the right side were unusually cellular, there being an increase in both Schwann cells and fibroblasts. The anatomic diagnosis was fibrosarcoma of the sphenoid bone with extension into the sphenoid and cavernous sinuses.

This case indicates the difficulty in differential diagnosis between a lesion in the cavernous sinus and one in the sphenoidal fissure. It is frequently stated that proptosis and orbital edema are more commonly found when the cavernous sinus is involved. However, in this case these ophthalmic signs were not observed, even though the sinus was almost obliterated at the time of necropsy. Other helpful points in the diagnosis of lesions of the cavernous sinus are involvement of the maxillary division of the trigeminal nerve, which leaves the skull through the foramen rotundum rather than the sphenoidal fissure, and roentgenographic evidence of destruction of adjacent bony structures. When the sphenoidal fissure is the site of the pathologic process, proper roentgenograms of the orbit may show widening of the fissure or destruction of its wall.

GUTTMAN, Philadelphia.

ISOLATION OF ST. LOUIS ENCEPHALITIS VIRUS FROM PERIPHERAL BLOOD OF HUMAN SUBJECT. R. J. BLATTNER and FLORENCE M. HEYS, *J. Pediat.* **28**:401 (April) 1946.

Blattner and Heys isolated a filtrable virus from the blood of a boy aged 8 years whose clinical manifestations were suggestive of a virus infection with minimal involvement of the central nervous system. The virus persisted in the peripheral blood approximately four days after onset of clinical symptoms. With the newly isolated strain of virus, parallel serum-virus neutralization tests were performed with blood serums obtained from the patient during the clinical course and with serums of rabbits immunized against a known St. Louis encephalitis strain of virus (Hubbard). Controls consisted of mixtures with broth alone and with normal human serum. The results of these tests showed that the infectious agent isolated is neutralized by the serum of a rabbit immunized to the known strain (Hubbard).

of the St. Louis encephalitis virus. During the clinical course the patient formed increasing antibody titer to the newly isolated virus and to known St. Louis encephalitis virus (Hubbard). Two criteria for the diagnosis of a virus disease have been satisfied, namely, isolation of an infectious agent from the patient and development during the course of clinical illness of type-specific humoral antibodies.

J. A. M. A.

CEREBRAL PALSY. E. STANLEY EVANS, *Proc. Roy. Soc. Med.* **39**:317 (April) 1946.

The rationale of treatment of patients admitted in the past three years to the Cerebral Palsy Unit at Queen Mary's Hospital, Carshalton, England, was founded on the principles originally laid down by Little and enunciated by Dr. Winthrop Phelps, of Baltimore, in his remedial school for spastic patients. These principles rest on the following basis: (1) an accurate diagnosis of the condition, i. e., whether the spasticity results from a lesion of the cerebral cortex, the underlying phenomenon being the spastic stretch reflex, or whether the cause lies in a tension athetosis, the tension representing a secondary result of an attempt to control the athetosis; (2) a careful mental assessment, to estimate the ability of the child to respond to teaching and training (less than 10 per cent of the athetoid children, but over 60 per cent of the spastic children, were found ineducable), and (3) a comprehensive, intensive and individually oriented therapeutic approach.

The obvious purpose of treatment is twofold: to estimate economic potentiality and to make the child independent, or at least semi-independent. Spastic patients are retrained by graded exercises until the spastic muscles can be utilized without the development of the spastic stretch reflex and improved tone of the weak muscles is attained. Resort to operation is made only when structural contractures are present.

Jacobsen's methods of conscious and voluntary relaxation are utilized to assist the athetotic patient in eliminating purposeless movements.

With the focus on individual training, besides the medical staff, a physical therapist, an occupational therapist, a speech trainer, an educational psychologist and a school teacher discuss the individual patients at weekly conferences.

Of 50 patients with cerebral palsy seen within the past few months, 32 were found to be educable. The results have far exceeded the author's expectation.

BERRY, Philadelphia.

Diseases of the Spinal Cord

MYELITIS FROM MUMPS. R. LIGHTWOOD, *Brit. M. J.* **1**:484 (March 30) 1946.

Lightwood reports a case of "local paralysis" resulting from mumps in a 16 year old youth. The clinical picture so strongly resembled poliomyelitis that this diagnosis would probably have been made were it not for the obvious evidence of mumps. The patient made an early and complete recovery.

ECHOLS, New Orleans.

ACTINOMYCOSIS OF THE THORACIC VERTEBRAE WITH PACHYMEMINGITIS AND COMPRESSION OF THE CORD. LAMARTINE DE ASSIS and MIGNONE, *Arq. de neuro-psiquiat.* **4**:21 (March) 1946.

A man aged 52 had been ill for two and a half years. The onset was insidious, with infected cervical glands, which broke down soon after the illness began. Increasingly severe backache soon appeared. The pain was dorsal and apparently radicular for about ten months, being worse with coughing and sneezing. During this time there were also progressive weakness in the lower limbs, occasional coughing and hemoptysis. The cutaneous lesions spread to the thorax. Examination on his admission to the hospital showed evidence of discharging lesions of the

skin, pulmonary infiltration, dorsal kyphosis and painful and enlarged liver. The spleen could be percussed easily. The blood pressure was 110 systolic and 70 diastolic. There was weakness of the lower limbs with exaggeration of the tendon reflexes and a bilateral Babinski sign; there were no sphincteric disturbances. The sensory examination was not reliable because of the patient's condition. Actinomyces were isolated from the discharging cutaneous lesions. Roentgenograms showed pulmonary infiltration and extensive destruction of the dorsal vertebrae. The spinal fluid was xanthochromic with no manometric block. Injection of iodized poppyseed oil revealed partial block with diffuse arrest of droplets, indicating the probable existence of leptomeningeal adhesions. Autopsy showed extensive actinomycosis of the lungs with purulent exudate in the soft tissues around the spinal column and in the bones. There was extensive thickening of the dura mater with scattered spots of inflammatory exudate. The spinal cord was intact. The pachymeningitis caused a myeloradicular syndrome without actual involvement of the cord. The authors report this complication as the first of its type in the Brazilian literature.

N. SAVITSKY, New York.

SURGICAL TREATMENT OF REFRACTORY SCIATICA DUE TO HERNIATED DISK. A. GARCIA FRUGONI, Rev. Asoc. méd. argent. 59:763 (July 15) 1945.

The author's observations are based on 35 cases of verified herniated disk and 7 cases of tumor of the cauda equina. In most cases the herniated disk was between the fourth and the fifth lumbar vertebra or between the fifth lumbar and the first sacral vertebra. The author favors a complete laminectomy, with wide and clear visualization of the operative field. When the dura is opened, bulging in the anterior part of the operative field is observed. A small incision at the site of this bulge usually localizes the disk. The articular facets were spared in all cases. There was no impairment of motion of the spine in any of the cases; no orthopedic measures were necessary to reenforce the spine. All the patients returned to work and were able to continue without reduction of efficiency. The author recommends always cutting the affected root in order to minimize the possibility of recurrence of radicular pain. The root is usually observed to be enlarged, edematous and congested and is sometimes covered with fine exudate. Because of overlapping of root segments, sensory sequelae do not persist after rhizotomy. Garcia Frugoni recommends the intrathecal injection of contrast medium in order to demonstrate and localize the herniated disk.

N. SAVITSKY, New York.

Peripheral and Cranial Nerves

DISTURBED VESTIBULAR FUNCTION. MARVIN F. JONES, Arch. Otolaryng. 41:272 (April) 1945.

The symptoms of vestibular irritation listed in the literature are nystagmus, vertigo and ataxia. There are approximately thirty-five known causes of these symptoms. Vestibular irritation may be due to nonsuppurative involvement of the labyrinth or to infection, local or general. Pus inside the labyrinth prevents any response to stimulation. A labyrinth surrounded by pus or secondarily involved in an inflammatory process will still respond to stimuli. The author was successful in curing many patients of their labyrinthine symptoms by removing the infected cells surrounding the labyrinth, using the postauricular incision for radical mastoidectomy. In other patients better results were obtained by using an endaural approach to the cells.

Jones reports on 3 patients who were not cured of their symptoms. The first was a man aged 48 who had right-sided facial paralysis for two years before roentgenograms were made, revealing extensive absorption of the petrous ridge from the labyrinth to the apex and absence of the lower half of the mastoid cells.

Five years later, he had exacerbation of his chronic mastoiditis, and an endaural exploratory operation was performed. Extensive destruction of bone and a nerve defect in the facial nerve were encountered. The patient did not respond well until sulfadiazine was administered into the spinal fluid and the wound packed with sulfathiazole paste. He finally recovered but still had paralysis of the right vocal cord, hoarseness and facial paralysis. The second case was that of a woman who, after several attacks of acute otitis media over a period of years, had had a discharging ear, vertigo and tinnitus for thirteen years. She had impaired hearing in the right ear and complained of falling to the right. An endaural mastoidectomy revealed a pathologic exposure of the dura of the middle fossa, exposure of the facial nerve and necrosis of the labyrinthine wall with exposure of the membranous labyrinth. She improved for several months but had a recurrence of her symptoms. It was then believed that the osseous lesion was tuberculous, in view of the fact that the patient had a pulmonary lesion which was arrested several years earlier. The third case was that of a man who showed symptoms of petrositis and labyrinthine involvement. Endaural removal of the perilabyrinthine cells relieved his symptoms, but they recurred.

The author believes that removal of perilabyrinthine cells should be attempted to relieve symptoms indicating inflammatory labyrinthine involvement other than diffuse suppurative labyrinthitis before the labyrinth itself is operated on.

RYAN, Philadelphia.

LABYRINTHITIS FOLLOWING PURULENT INFECTION OF THE MIDDLE EAR. FRANZ ALTMANN and JULES G. WALTNER, Arch. Otolaryng. 42:93 (Aug.) 1945.

A thorough knowledge of the genesis of labyrinthitis, as an aid in the prevention of hearing defects due to labyrinthine infection, is still desirable in spite of recent chemotherapeutic advances. Detailed histopathologic studies of many cases have shed much light on the pathway of infection, although it cannot always be definitely traced.

Altmann and Waltner describe 5 cases in which hemolytic streptococci were the cause of tympanogenic labyrinthitis. In each case death was caused by labyrinthogenic meningitis. In 1 case the labyrinthitis followed acute otitis media; in 3 cases, an acute exacerbation of chronic otitis media, and in 1 case, chronic otitis media with cholesteatoma. From a study of the clinical course and the histologic examinations, the authors analyze the role of the oval and round windows in the genesis of labyrinthine changes. In acute exudative otitis media or in acute exacerbations of uncomplicated middle ear infection, extension of the pathologic process usually occurs through one or both windows. It cannot be definitely stated from the information at hand just which of the two windows is more often the portal of entry or in how many instances the infection penetrates through both windows simultaneously. Because the histologic changes occurring in primary invasion of the windows are identical with the secondary reactive changes following a purulent labyrinthine infection through another portal of entry, clearcut interpretations are often difficult to obtain. The unfavorable conditions of drainage, due to the anatomic structure of the labyrinth, facilitate the development of leptomeningitis. The resistance of the mucosal covering of the window membranes to destruction further impedes drainage to the middle ear.

The character of the underlying infection of the middle ear largely determines the genesis of labyrinthitis. Exudative inflammations, as a rule, spread through the windows; proliferative infections (*Pneumococcus* type III) and chronic infections complicated with cholesteatoma, through the osseous capsule, particularly the semi-circular canals. The character of the labyrinthitis is not determined by the character of middle ear infection. The most important pathway of extension of infection to the meninges is along the channels of the modiolus and the vestibule. In 4 of the 5 cases here reported the infection spread through the modiolus.

Although the question of the pathways of endocranial extension of infection has lost some of its importance since recent chemotherapy has been used with such success, it still deserves attention for the sake of the complications that will undoubtedly persist in spite of chemotherapy.

RYAN, Philadelphia.

PRIMARY SUTURE OF NERVES. R. B. ZACHARY and W. HOLMES, Surg., Gynec. & Obst. **82**:632 (June) 1946.

Zachary and Holmes review cases of primary nerve suture which came under observation at the center for peripheral nerve injuries at the Wingfield-Morris Hospital, Oxford, England, from 1940 to 1944. There were 55 cases of primary nerve suture. The results in these cases are compared with results in cases of early secondary suture. Contrary to the widely accepted view, the proportion of good results is higher for early secondary suture than for primary suture. Sepsis was not the chief adverse factor involved in primary suture. Microscopic examination of the site of primary suture in 16 cases indicated that the chief faults were poor technic, inadequate resection of the damaged nerve ends and excessive postoperative tension. There is a great deal to be gained by approximating the ends of the divided nerve to prevent retraction. When secondary suture is performed in a few weeks, the length of nerve to be resected will probably be short; the suture can be performed with precision and without tension, and the prospects of recovery will be good. If deliberate primary suture has been performed, the patient should be watched carefully. If progress appears unduly slow, further resection and resuture should be considered.

J. A. M. A.

THE MARCUS-GUNN SYNDROME. J. L. WELLS, U. S. Nav. M. Bull. **46**:1275 (Aug.) 1946.

Wells reports a case of the Marcus-Gunn syndrome in a white Marine aged 25 which was discovered incidentally in routine physical examination. The family history was not remarkable. The personal history revealed the presence of ptosis and associated winking of the left eyelid in talking and eating since infancy. Except for the syndrome, the general physical condition was normal. The reflexes, sensory status, pupillary reactions and extraocular movements were normal, as were the corneal reflexes and the facial muscles. There was ptosis of the left eyelid. When the mouth was opened wide and the mandible moved to the right, a pronounced elevation of the left upper eyelid occurred. Movement of the mandible to the left failed to elicit the response. As in the majority of cases reported, the movements of the eyelid occurred on contraction of the ipsilateral external pterygoid muscle.

The general varieties of this syndrome are (1) unilateral ptosis, in which the eyelid is raised (a) when the mouth is opened and the mandible is moved to the opposite side, (b) when the mouth is opened but not when the mandible is moved laterally and (c) when the mandible is moved to the opposite side but not when the mouth is opened; and (2) associated movements of the eyelid and jaw without ptosis. Further bizarre associated movements have been reported.

The etiologic factor is obscure, and treatment save for cosmetic and emotional reasons is not indicated.

BERRY, Philadelphia.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Kenneth J. Tillotson, M.D., *Presiding*

Regular Meeting, March 21, 1946

Effect of Penicillin on the Central Nervous System. DR. HERBERT C. JOHNSON, DR. A. EARL WALKER, DR. THEODORE J. CASE and DR. JERRY J. KOLLROS, Chicago.

This paper appeared in full in the ARCHIVES (56:184 [Aug.] 1946).

DISCUSSION

DR. AUGUSTUS R. ROSE, Boston: It is a pleasure for those of us who know Dr. Walker's writings to have him present this fine paper. My experience with the use of penicillin has been confined to investigations on neurosyphilis. As many of you know, there has been considerable pressure for the intrathecal use of penicillin in treatment of neurosyphilis. Prior to the publication of Neyman, referred to by Dr. Walker, which showed the dangers of large doses of penicillin given into the spinal fluid, we at the Boston Psychopathic Hospital gave penicillin to 5 patients by this route. In all cases the dose was less than 10,000 units. In none of these patients was there any evidence of muscular twitchings or convulsions: Fortunately, evidence is accumulating to show that intrathecal administration of penicillin is not necessary in cases of neurosyphilis, although it is indicated in a few cases of purulent meningitis.

I should like to ask Dr. Walker two questions: 1. Has he any idea as to the mechanism whereby the antibiotic substance acts to produce the convulsions? 2. Was the crystalline penicillin used fraction G, K or X?

DR. WILLIAM H. SWEET, Birmingham, England: I wish to join in congratulating Dr. Walker on this fine presentation. Having had reports of Dr. Walker's work while it was still in progress, I have watched especially for convulsions in cases of meningitis treated with penicillin. In a group of patients seen when there was only enough penicillin available to give it intrathecally, I saw no convulsive seizures, despite what I felt to be the necessity of giving moderately large doses. A maximum of 20,000 units was given into the cerebrospinal fluid at one time. Some patients with meningitis had the tremors of low amplitude typical of the condition before penicillin was given, and these movements were not exacerbated by the penicillin. Many patients whom I gave intrathecal injections mentioned experiencing a diffuse sensation of warmth at the time. During intracisternal injections of penicillin the warm feeling was likely to be referred to the whole head, whereas during lumbar injections the lower part of the back felt warm.

Recently, at the Massachusetts General Hospital, streptomycin was given to a small child under 1 year of age with meningitis due to *Proteus vulgaris*. Repeated doses had no convulsant effect, but they were sufficient to clear up the meningitis entirely and leave no sequelae.

I should like to emphasize Dr. Walker's statement that as long as penicillin and streptomycin are used only in doses that are known to be lethal to the organisms usually classified as sensitive to their action no untoward convulsive effects will occur.

DR. ROBERT S. SCHWAB, Boston: I should like to add my word of congratulation on the development and isolation of this material, which appears to be strongly

convulsant in the huge doses used in this study. I saw a patient on Guam with a severe fungous infection of the brain from a shell wound. Penicillin was used intravenously and locally in large amounts. I have no idea of the total amount of penicillin given. After injection he had an acute confusional episode, was disoriented and violent and had a rise in temperature. There was nothing to suggest epilepsy, and there was no focal discharge. This episode lasted twenty-four hours. Local injection of penicillin was discontinued. He improved. Could this delirium be due to the penicillin?

DR. WILLIAM G. LENNOX, Boston: I should like to ask a question along a similar line. In the case of a patient with a low seizure threshold, an epileptic patient for example, is there any evidence that penicillin given intravenously might activate his seizures? I should like to see an enlargement of the tracings shown on the screen. Some of the convulsions were what clinically would be called myoclonic jerks, and I wonder whether there were any accompanying wave and spike formations in the electroencephalograms. This study has added another substance to the many already known which can cause convulsions. These observations offer an increasing number of leads which, if tracked down, might increase the knowledge of epilepsy. It is interesting that these patients present no pathologic changes.

DR. A. EARL WALKER, Chicago: I am grateful to the discussers for their comments.

We used the penicillin manufactured by ten companies, and we could see no difference in the convulsive effect of the ten products. They all seemed to have essentially the same convulsive effect.

It is quite true that clinically one does not see convulsive manifestations when therapeutic doses are given. One reason is that the amount of penicillin which reaches the cerebral cortex when injected in the lumbar region is only approximately 1 per cent of the dose given. Assuming that 20,000 units was injected, only 200 units gets to the cisterna magna, and 200 units is less than the convulsive threshold dose. The amount over the surface of the brain is still much less than that. We have injected very large amounts of penicillin into the ventricular system, as much as 100,000 units, without producing convulsions. There is, therefore, a great individual variability. I do not know the neural mechanism of the convulsive attacks due to penicillin or the other antibiotic substances.

We did not see the typical wave and spike formations in the electroencephalogram, which, as Dr. Lennox mentioned, are typical of certain types of idiopathic epilepsy. In the majority of the cases the convulsion consisted of a series of spikes, rather than of humps and spikes.

Military Neurology in India with Especial Reference to Deficiency Syndromes in Ex-Prisoners of War. DR. D. DENNY-BROWN.

After comments on the climate and on the composition of armies in India and Burma, the military medical organization was described. Incidental observations confirmed the absence of multiple sclerosis, although diseases such as amyotrophic lateral sclerosis and muscular dystrophy were seen. Meningovascular syphilis was common, but tabes and dementia paralytica were extremely rare. The syndrome of prolapsed intervertebral disk was common among Europeans in India, but scarcely a case was known in Indian nationals. Classic causalgia was a relatively common accompaniment of injuries of the median and popliteal nerves, and there was some evidence that the increased incidence was related to the combined humidity and heat. Cutaneous diphtheria was a problem in jungle warfare, and penetrating jungle head wounds carried a high rate of infection with *Bacillus coli*. Cysticercosis was seldom seen in the stage of recent invasion, but there was reason to believe that many men were infected. It should be suspected in any soldier in whom epilepsy develops in two to five years after service in India. The hyperpyrexia following heat stroke led to a cerebellar syndrome in some men, and it was considered that hyperpyrexia was the mechanism of the similar ataxia which

was occasionally seen after cerebral malaria. Poliomyelitis was a troublesome problem in 1945, affecting chiefly young men recently arrived in India, even in areas where elaborate precautions against insect transmission had greatly reduced insect-borne diseases. Fecal contamination of water supplies was notorious throughout the East, and it was felt that insistence on decontamination of feces in all known cases of poliomyelitis with more effective disinfectants than the usual "lysol" (saponated solution of cresol U. S. P.) should be made general practice.

Among the prisoners of war released from Rangoon there were, besides cases of "famine edema" and a few residual cases of beriberi, many cases of amblyopia due to retrobulbar neuritis. When severe, this condition was associated with ataxia and deafness. This condition was described in Malaya by Landor and Pallister (*Tr. Roy. Soc. Trop. Med. & Hyg.* 29:121 [July] 1935) and is certainly a deficiency syndrome. With the release of prisoners of war from Malaya, Batavia, Siam and Indo-China, many more cases of this condition were seen; in addition, a condition of spastic paraplegia resembling lathyrism was observed. The nature of these conditions was discussed and illustrated.

DISCUSSION

DR. HERRMAN L. BLUMGART: Since returning from India, I have wanted to make another visit but did not anticipate as charming and fascinating a "return" as that this evening. As Dr. Denny-Brown says, it is a country of sharp contrasts. It is too rich and too poor, too hot and too cold, too wet and too dry.

The British plan in regard to consultants was far superior to the American. Our outfit had only three consultants—medical, surgical and neuropsychiatric. American forces were deployed in Burma, India and China. During the year, we were traveling a good deal of the time by airplane. The experience we had was dissimilar to Dr. Denny-Brown's in that we saw no vitamin deficiencies except in prisoners of war who came in from China and Burma.

My interest was primarily medical. I saw practically every tropical disease in the textbooks. Amebiasis was the most urgent problem. Of the conditions that might interest you there were several. Cutaneous diphtheria was first to be recognized in Burma. It was chiefly diagnosed as oriental sore and was then suspected to be beriberi. Several patients died of congestive failure, and the disease was recognized. It was one of the very important medical conditions in the Burma campaign. Poliomyelitis was particularly virulent and fatal, with high frequency of the bulbar type and a mortality rate of 40 per cent. Fortunately, the disease was not prevalent. Among the Chinese troops in Burma, cerebral malaria was frequent. Filariasis was difficult to diagnose. We saw approximately 20 cases of smallpox a year, although our men had been vaccinated. We had little cholera, although while I was in Chungking there were 80,000 cases among the civilian population. With proper educational measures and vigilance, the incidence of cholera was reduced to practically nil. Only 20 cases occurred in the last few months, and these were of men who drank some "crystal clear water" near an infected village. With the advances in chemotherapy these diseases have lost their horror. The mortality of cholera has usually varied from 40 to 60 per cent, but with the use of intravenous administration of fluids, transfusions, sulfadiazine and penicillin it can evidently be reduced to 2 per cent.

The climate is just as Dr. Denny-Brown described it, but no one spending a period of time in India can fail to look back on it as an extraordinary personal experience and an even more fascinating professional experience.

DR. ROBERT S. SCHWAB: The part of Dr. Denny-Brown's talk which impressed me most was that which revealed the patience and skill with which he collected all this material. Many of us in the service traveled thousands of miles and had interesting clinical experience, but we did not succeed in keeping accurate notes—we have only vague memories. I am greatly impressed with the completeness of these observations and their value to clinical neurology.

In August and September I had an opportunity, as neurologist in a naval hospital in Guam, to examine 960 evacuees, American and British prisoners of war who had been in prison camps for three years. They had been moved in 1943 and 1944 under atrocious conditions to Japan, near Tokyo. This group represented mostly ambulatory patients sent to the naval hospital to get a week of complete examinations—neurologic, psychiatric and electrocardiographic and other laboratory studies. The results of these examinations are in line with what Dr. Denny-Brown has presented. My colleagues and I saw for the first time—and it was rather new to our ophthalmologist—patients with retrobulbar neuritis. Ten per cent of these patients showed varying degrees of visual loss with central scotoma and atrophy around the macula. We wondered whether they would regain the vision that they lost during the period in which they were on a deficient diet. They were given an adequate diet with the addition of large amounts of vitamin B complex. Some of the losses of weight were amazing to me—from 75 to 80 pounds (34 to 36.3 Kg.) in men from Corregidor—but the patients gained back from 5 to 10 pounds (2.3 to 4.5 Kg.) a week. Thirty per cent of these men gave a history of beriberi on the interview questionnaire, but I think that two thirds of these men had nutritional edema instead. There were some ataxia and peripheral neuritis with residual loss of reflexes. Many complained of painful feet. I saw some cases of paraplegia with spastic reflexes. The patients had been bedridden for long periods and had not received any form of medical treatment. We obtained electrocardiograms on the men; not many were abnormal. All the patients were reasonably young men, who should not have had any cardiac disease at their age.

I shall mention one form of treatment that I learned of, particularly among the Canadians from Hongkong and our men from the Chinese prison camps. The patients were bedridden and could not work. The Japanese doctors would make a diagnosis of "wet beriberi" and then use the gunpowder treatment. A pile of gunpowder 2 cm. high was ignited over points along the distribution of the peripheral nerve; the burn caused an indurated ulcer, which persisted several months. It was thought at first that this was a form of torture, but it was done in so many different camps in cases of peripheral neuritis that I wonder what the explanation really was.

I talked with some of the doctors who were with these men, and they told me the Japanese had vitamin compounds for sale. On hospital ships they were able to make assays of these vitamin compounds, which were found to be inert. The products were commercial preparations on sale throughout Japan. From this group of patients we obtained the information that the spring of 1942 was the worst with respect to neurologic disease and symptoms. The diet was extremely poor; but it improved in 1944, and an effort was made to prevent nutritional disease. In 1945 the diet was somewhat improved, so that deficiency diseases would not interfere too much with the use of the men as workers. Many worked north of Tokyo in coal, zinc and lead mines for fifteen hours a day. When one saw these men, 50, 60 or 70 pounds (22.7, 27.2 and 31.8 Kg.) underweight, one wondered how they could have worked under such conditions, with painful and swollen feet. I saw only 2 men out of 960 whom I thought had a neurosis. The medical officers whom I talked with, who were also prisoners, said that the psychopathic and neurotic prisoners had died of cold, heat, starvation and beatings in the struggle for survival of the fittest. The men with unstable personalities among the prisoners died first, so that the percentage of neuroses among the men who came back was small. The Japanese were afraid of psychotic prisoners; often violent ones were allowed to escape, and some were shot when they tried to come back. The officers who were prisoners of war had an easier time in that they were excused from hard labor. Their great trouble was idleness. The hobbies that they developed would make an interesting paper in itself.

I think this society is fortunate to have heard this interesting paper.

DR. D. DENNY-BROWN: With respect to the prognosis of nutritional retrobulbar neuritis, I can say that with intramuscular injections of liver extract the

patients with the mild form recovered in four to six weeks. The patients with vision reduced to 50/100 might recover near-normal vision; those with a reduction to 80/100 usually recovered only 50/100 vision. The severer types might be expected to leave residual structural changes.

Beriberi is a recoverable disease. Recovery is slow and steady with treatment, and undoubtedly the condition had been very common. Most of the patients had recovered before I saw them, but the absence of ankle jerks and tenderness might persist for six months after recovery of motor function.

Of the gunpowder treatment I know nothing, except that it is reputed to be an old Chinese treatment. Vitamin pills had been provided at times by the Japanese, and some were certainly potent; but the Japanese also had large stocks that they had failed to issue.

Frank neurosis was uncommon—I do not know why, whether by elimination of the unfit or for some other reason. My colleagues and I had a series of 27 psychotic men who had been through the period in the Changi camp and had had excellent care.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

Thomas J. Heldt, M.D., *President, in the Chair*

Regular Meeting, Eloise, Mich., Dec. 5, 1946

Laurence-Moon-Biedl Syndrome. DR. JOSEPH SLUTZKY, Eloise, Mich.

The case was reported of a Negro aged 40 with polydactyly, retinitis pigmentosa and mental retardation. This unusual syndrome was first described by Laurence and Moon in 1866.

Five Year Results of Shock Treatment: A Follow-Up Study. DR. EDWARD N. HINKO and DR. LOUIS S. LIPSCHYTZ, Detroit.

In attempting a critical evaluation of the shock therapies, including the insulin coma method, the metrazol convulsion method and the electric shock method, 457 treated patients were compared with a control group of 289 patients. In this study the percentages of paroles, relapses, reparoles and paroles at time of the study were utilized. A comparison of the average periods of hospitalization for treated and for untreated patients was made, and the preliminary results of a follow-up study of patients on parole from both the treated and the untreated group was reported.

It was found that a higher number (9 per cent) of remissions may be expected after shock therapy than when remission is permitted to occur spontaneously. The study also revealed that treatment given during the first year of residence in hospital results in the saving of four hundred and twenty-two hospital days per patient, remission permitting parole occurring in one-third the time required for spontaneous remission.

Prefrontal Lobotomy for Severe Conduct Disorder. DR. ROBERT M. JENNINGS, Eloise, Mich.; DR. AAGE NIELSEN, Detroit, and DR. MILTON H. ERICKSON, Eloise, Mich.

PRESENTATION OF CASE (DR. JENNINGS)

The patient, a young woman, had a long history of severe conduct disorder. Her antisocial conduct dated back to the age of 4 and included such problems as kleptomania, pyromania, oral and anal perversions, nomadism and alleged homicidal acts. Both before and after operation, the patient was given electroencephalographic and intensive psychologic study, including the Wechsler-Bellevue test, the Ellis Visual Memory Test, the Rorschach Personality Study and the Murray Thematic Apperception Test. An anterior leukotomy was done on Oct. 29, 1946. It was

concluded, five weeks after operation, that the leukotomy had brought about definite improvement in the patient's behavior pattern and personality. She apparently had lost the intense, impulsive preoperative drives which had resulted in a long history of overt, aggressive, antisocial behavior, and she appeared to be a quiet, emotionally subdued person. Further studies and continued observation on this case were indicated.

OPERATIVE PROCEDURE (DR. NIELSEN)

After preparation with soap, water, alcohol and "mercresin" (amyltricrosols and orthohydroxyphenyl mercuric chloride), injection of 1 per cent procaine hydrochloride was carried out over the area of the proposed incisions. One inch (2.5 cm.) incisions were made equidistant from the midline, about 3.5 cm. anterior to a plane through the external acoustic meatuses and about 3 cm. from the midsagittal suture. The incisions were carried down through the subcutaneous tissue and the galea, exposing the coronal suture on each side. The wounds were held open by mastoid retractors. With a circular saw, a button of bone the size of a quarter was removed on each side. The underlying dura was incised and held back with guy sutures. On the right side the pia-arachnoid was then incised and a ventricular needle inserted in the direction of the lesser wing of the sphenoid bone. The needle was then reinserted somewhat farther posteriorly and the middle fossa was entered, thus giving a definite landmark and assurance that the anterior horn of the lateral ventricle had not been entered. With the ventricular needle as a guide, the frontal association fibers were severed by cutting with a blunt instrument downward, medially and laterally. With use of the blunt instrument and fine suction, it was possible to make a complete sweep from side to side and sever practically all the white fibers from the frontal lobe to the thalamus.

Care was taken to avoid the cortical gray matter itself, and large vessels, including the anterior cerebral arteries, were watched for and avoided. During the dissection down to the brain a good view was obtained at all times by means of ribbon retractors inserted into the brain itself. The comparatively little bleeding which occurred during the procedure was easily controlled with the coagulating current.

The same procedure was carried out on the left side.

After complete hemostasis, the wounds were closed with interrupted silk sutures, applied first to the dura; then the buttons of bone were reinserted, and interrupted sutures were applied to galea and skin.

After the second stage of the procedure the patient became somewhat disoriented and drowsy, but the strength of the right hand and her capacity for speech were still present. The patient was then returned to the ward, apparently in good condition.

PSYCHODYNAMIC STUDY (DR. ERICKSON)

The psychodynamic aspects of the patient's obsessive-compulsive criminalistic behavior were discussed in terms of the patient's own remarkable, but unorganized, purely intellectual, insight into her conduct. The primary dynamisms were those of profound rejection of the self and strong destructive attitudes toward society.

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following certifications were made at the meeting of the Board in Philadelphia, May 15-17, 1947:

Psychiatry.—By Examination: Solomon Adelman, Northport, N. Y.; Albert H. Argent, Marion, Ind.; Clinton Harry Bagenstose, New York; James Louis Baker, Forth Worth, Texas; Milton Charles Baumann, Sprigfield, Ill.; Eleanor Beamer-Maxwell, Williamsburg, Va.; William Peter Beckman, Columbia, S. C.; John A. Belisle, Eloise, Mich.; H. Craig Bell, Abington, Pa.; Raymond J. Bennett, Tacoma, Wash.; Nathan K. Bernstein, Utica, N. Y.; Siegfried R. Berthelsdorf, New York; Brian Bird, Toronto, Canada; Douglas D. Bond, Cleveland; Louis D. Boshes, Chicago; Chris J. Buscaglia, Ypsilanti, Mich.; Stuart K. Bush, Denver; Dale Corbin Cameron, Washington, D. C.; Joseph Anthony Cammarata, Dixmont, Pa.; Howard R. Campbell, Dayton, Ohio; Dominick J. Carlisi, West Brentwood, N. Y.; Arthur L. Chandler, Los Angeles; Frank E. Coburn, Iowa City; Samuel Cogan, Brooklyn; Max Cohen, Coatesville, Pa.; Arthur T. Colley, Lyons, N. J.; Henry S. Colony, Fort Worth, Texas; C. Archie Crandell, Greystone Park, N. J.; Bernard A. Cruvant, Washington, D. C.; C. Nelson Davis, Philadelphia; Alcinda P. de Aguiar, Bedford, Mass.; Stanley R. Dean, Stamford, Conn.; Samuel Dinenberg, Philadelphia; William C. Douglass, Palo Alto, Calif.; Lester Drubin, Northport, N. Y.; R. Stuart Dyer, Syracuse, N. Y.; Carl M. Epstein, Topeka, Kan.; David J. Fish, Howard, R. I.; Maria F. Fleischl, New York; John M. Flumerfelt, Cleveland; *David Bernard Foster, Topeka, Kan.; Kate Frankenthal, New York; Richard M. Free, Philadelphia; Henry Freund, Rochester, N. Y.; Robert S. Garber, Trenton, N. J.; Sol Weiner Ginsberg, New York; Sarah E. Glass, Worcester, Mass.; James S. Glotfelty, Sheridan, Wyo.; Gerald L. Goodstone, Syracuse, N. Y.; P. Goolker, New York; Thomas L. Greason, Providence, R. I.; Marvin F. Greiber, Muncie, Ind.; Maurice Grossman, Augusta, Ga.; Lloyd William Hatton, Salina, Kan.; John James Head, White Plains, N. Y.; Friedy B. Heisler, Chicago; Louis Herman, Fort Custer, Mich.; Thomas F. Hersey, New Haven, Conn.; Robert T. Hewitt, Fort Worth, Texas; Edward N. Hinko, Eloise, Mich.; Cotter Hirschberg, Denver; Gerhard Hirschfeld, Norwich, Conn.; Clarence S. Hoekstra, Denver; Oscar E. Hubbard, Dallas, Texas; Portia B. Hume, Berkeley, Calif.; James B. Hurley, Milwaukee; George W. Jackson, Little Rock, Ark.; Louis Jacobs, Mount Rainier, Md.; Franklin Johnson, Eloise, Mich.; Leopold Jordani, New York; Rudolph Kaldeck, Boston; Julius Arthur Kaplan, Northampton, Mass.; Samuel R. Kesselman, Brooklyn; Isham Kimbell Jr., Fort Custer, Mich.; Harold N. King, Hampton, Va.; Joseph L. Knapp, Weston, W. Va.; Salmon A. Koff, Mendota, Wis.; Louis Koren, Eloise, Mich.; Samuel H. Korman, Brooklyn; Elinor M. Langton, Philadelphia; Ulrich Ledien, Peoria, Ill.; George Leventhal, Los Angeles; Samuel Levin, Philadelphia; Stanley B. Lindley, Willmar, Minn.; Harry H. Lipcon, Portsmouth, Va.; Sam J. Lipkin, Chicago; Samuel D. Lipton, Chicago; LeRoy M. A. Maeder, Philadelphia; Vincent P. Mahoney, Philadelphia; Joseph A. Manno, Central Islip, N. Y.; Thomas A. March, Poughkeepsie, N. Y.; Samuel H. Marder, Boston; Joseph H. Marshall, Sykesville, Md.; *Richard L. Masland, Winston-Salem, N. C.; Frederick Mayer, Louisville, Ky.; Jay Earl McCormick, Chicago; Gladys McDermid, Brooklyn; Francis McLaughlin, Baltimore; Carl Miller, Kankakee, Ill.; Harry Moscowitz, New York; Raymond Nadell, Brooklyn; Kenneth C. Nickel, Ypsilanti, Mich.; Mervyn M. Nickels,

Traverse City, Mich.; Richard H. Parks, Warren, Pa.; Roy A. Phillips, Hines, Ill.; Edgar Lee Porter, Wayne, Pa.; Florence Powdermaker, Washington, D. C.; George S. Rader, Bloomington, Ind.; * Stephen W. Ranson, Baltimore; Samuel Reznick, Los Angeles; Sol A. Robins, Amityville, N. Y.; Milton H. Rodofsky, Boston; Roland D. Roecker, Millington, N. J.; William R. Rosanoff, Alhambra, Calif.; Morris M. Rosenthal, Chicago; Daniel M. Rosman, Topeka, Kan.; Emanuel Rubin, Canandaigua, N. Y.; Thomas A. Ruddell, Allentown, Pa.; Julius Rudnick, Brooklyn; Benno Safier, Agnew, Calif.; George Saslow, St. Louis; James P. Scanlon, Llanerch, Pa.; Gerhard Schauer, Floral Park, N. Y.; Ber M. Schegloff, Boston; Rosa B. Schub, Trenton, N. J.; Bruno G. Schutkeker, Buffalo; Emmanuel Silver, Palo Alto, Calif.; Jacob Sirkin, Newark, N. Y.; Charles A. Smith, Oklahoma City; Stewart R. Smith, Quincy, Mass.; Bernard S. Stell, Buffalo; Marvin Stern, Brooklyn; H. Gordon Stratton, New Toronto, Ontario, Canada; Theodore P. Suratt, Cleveland; Florence L. Swanson, Seattle; David R. Talbot, Los Angeles; Thomas Thale, St. Louis; Charles W. Tidd, Beverly Hills, Calif.; Oswald V. Todd, Washington, D. C.; Leo Milton Traub, Palo Alto, Calif.; Max Unger, Middletown, N. Y.; Robert J. Van Amberg, East Orange, N. J.; Abraham L. Waldman, Norristown, Pa.; Guy M. Walters, Willard, N. Y.; Benjamin Wassell, Greystone Park, N. J.; Max E. Witte, Portland, Me.; Ralph I. Wolfe, Toronto, Canada; Horatio C. Wood, Peoria, Ill.; Richard V. Worthington, Framingham, Mass.; Donovan G. Wright, Great Lakes, Ill.; Harold S. Wright, New York; Miltiades L. Zaphiropoulos, New York; Ladislaus J. Zbrank, Fort Worth, Texas.

Psychiatry.—On Record: Neil D. Black, Marcy, N. Y.; Frederick M. Cook, Lexington, Ky.; Clarence M. Crawford, Kingston, Ontario, Canada; George E. Charlton, Norfolk, Neb.; Harry Elkins, Augusta, Me.; Earl W. Fuller, Greystone Park, N. J.; Joe Funderberg, Torrance, Pa.; John Herbert Hare, Evansville, Ind.; Anita W. Harper, Harrisburg, Pa.; Sidney Klein, New York; Hyman L. Levin, Buffalo; John Francis McNeil, Beacon, N. Y.; John A. P. Millet, New York; Bryant Edward Moulton, Winchester, Mass.; Ione Pinney, Stockton, Calif.; James P. Sands, Millville, Pa.; Abram J. Spor, Middletown, N. Y.; John F. Stouffer, Philadelphia; Louis F. Verdel, Northport, N. Y.; Ray L. Whitney, Waverley, Mass.; George W. Wilson, Chicago.

Neurology.—By Examination: Kenneth Harvey Abbott, Columbus, Ohio; Pearce Bailey, Washington, D. C.; Ruth I. Barnard, Topeka, Kan.; * Samuel Cohen, Philadelphia; Justin L. Greene, New York; * Benjamin H. Kagwa, Chicago; * Jacob Lerman, Brooklyn; * Robert L. Meller, Minneapolis; J. Peter Murphy, Washington, D. C.; Hugh Page Newbill, Staunton, Va.; * Leon L. Rackow, Tuscaloosa, Ala.; Edward P. Roemer, Madison, Wis.; Jack George Sheps, Orangeburg, N. Y.; * Stephen C. Sitter, Washington, D. C.; Eli L. Tigay, Chicago.

Neurology.—On Record: Charles S. Kubick, Boston; Milton K. Meyers, Philadelphia; Ignatius N. W. Olinick, New York.

Neurology and Psychiatry.—By Examination: Helen Blake Carlson, Chicago; Elic A. Denbo, Camden, N. J.; Edward Gendel, New York; Major Albert J. Glass, M.C., A. U. S., Augusta, Ga.; Bernard Goodman, Miami Beach, Fla.; Harrington V. Ingham, Los Angeles; Samuel S. Kaufman, New York; Albert E. Rauh, Lyons, N. J.; Harry A. Teitelbaum, Topeka, Kan.

Neurology and Psychiatry.—On Record: George E. Price, Seattle.

* Denotes complementary certification.

CERTIFICATIONS TO AMERICAN BOARD OF NEUROLOGICAL SURGERY

At its meeting in Chicago, June 3 to 5, 1947, the American Board of Neurological Surgery issued its certificate to the following candidates*: Frank M. Anderson, Los Angeles; Robert B. Bassett, St. Louis (May 1, 1947); Leon L. Bernstein, Topeka, Kan.; Howard A. Black, Sacramento, Calif.; August Buermann, South Orange, N. J.; James B. Campbell, Boston; Herbert G. Crockett, Los Angeles; Henry M. Cuneo, Los Angeles; Edward W. Davis, San Francisco; Arthur R. Elvidge, Montreal, Canada; Abraham Ettleson, Los Angeles; Emanuel H. Feiring, New York; Arthur I. Finlayson, Omaha; John D. French, Rochester, N. Y.; O. Hugh Fulcher, Washington, D. C.; Hugh W. Garol, San Jose, Calif. (Sept. 1, 1947); J. Worden Kane, Binghamton, N. Y.; Erich G. Kreuger, New York; Vasilios S. Lambros, Washington, D. C.; Peter Lehmann, Vancouver, British Columbia, Canada; Edgar S. Lotspeich, Cincinnati; Collin S. MacCarty, Rochester, Minn.; Hunter J. Mackay, Seattle; Juan de Dios Martinez-Galindo, Charlottesville, Va. (May 1, 1947); Harry P. Maxwell, Milwaukee (Oct. 1, 1947); W. B. Patton, Birmingham, Ala.; Raymond H. Quade, Neenah, Wis.; Robert Raskind, Memphis, Tenn.; Henry A. Shenkin, Philadelphia; Alfred Uihlein, Rochester, Minn.; Philip J. Vogel, Los Angeles; Exum B. Walker, Atlanta, Ga.; Willard B. Weary, Dallas, Texas; Arthur A. Wilson, Charleston, W. Va.; Jack I. Woolf, Dallas, Texas.

*The date of certification, unless otherwise indicated in parentheses, was June 1947.

POLIOMYELITIS CONFERENCE, WARM SPRINGS, GEORGIA

A three day clinical conference on the diagnosis and treatment of poliomyelitis will be held at Warm Springs, Ga., on September 15, 16 and 17, the twentieth anniversary of the founding of Georgia Warm Springs.

The clinical conference will be led by approximately twenty of the nation's authorities in the fields of neurology, pathology, pediatrics, orthopedics, physical medicine and internal medicine, who will present papers reviewing the advances in knowledge of poliomyelitis in these fields.

The papers and discussions will constitute a new book on diagnosis and treatment of the disease, for publication in 1948. Clinical demonstrations of modern treatment methods will be given by the medical staff of the Georgia Warm Springs Foundation.

Physicians interested in attending this conference should address inquiries to the Georgia Warm Springs Foundation, 120 Broadway, New York 5. A complete program of the meeting will be available on request.

AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

At the seventy-first annual meeting of the American Association on Mental Deficiency, held in St. Paul, May 27 to 31, the following officers were elected: president, Dr. Lloyd Yepson, Trenton, N. J.; president elect, Dr. Edward J. Humphreys, Columbus, Ohio; secretary-treasurer, Dr. Neil A. Dayton, Mansfield Depot, Conn.; editor of journal, Dr. Edward J. Humphreys. •

Final plans were outlined for the First International Congress on Mental Deficiency, which will be held in Boston, at the Hotel Statler, May 11 to 15, 1948. This meeting is to commemorate the first American institution for mentally defective persons; established in Boston in 1848. It is anticipated that there will be delegates and speakers from North and South America, the British Isles, Europe, Australia and New Zealand. The chairman for the committee on arrangements is Dr. C. Stanley Raymond, Wrentham, Mass.

Obituaries

EDWARD BOYNTON ANGELL, M.D.

1856-1947

Dr. Edward Boynton Angell, for many years active in neurology in central New York state, was born on Oct. 30, 1856, at McLean, N. Y., the son of Edward and Austana (Boynton) Angell. He received his preliminary education in the public schools of Binghamton, N. Y., and the Waverly High School. In 1877 he was graduated from the University of Rochester with the degree of Bachelor of Arts and entered the University of Pennsylvania School of Medicine, from which he received his medical degree in 1881.

After his graduation he served an internship in St. Mary's Hospital, Philadelphia, and in the Philadelphia Infirmary for Nervous Diseases from 1882 to 1883, where he worked closely with Dr. Weir Mitchell. Leaving Philadelphia in 1883, Dr. Angell opened an office in Rochester, N. Y., where he practiced as a neurologist until his retirement in 1933.

Dr. Angell was one of the founders of the Rochester Academy of Medicine and for a while served as president of that organization. In 1903 he was elected vice president of the Medical Society of the State of New York. He also served a term as president of the Medical Society of Central New York. In 1891 Dr. Angell was elected to the American Neurological Association and served as vice president in 1907. After his retirement he went to live in Cold Spring, N. Y., where he could indulge in his great hobby of trout fishing. On April 23, 1947 Dr. Angell died rather suddenly, of a cerebral hemorrhage. He is survived by a son and three grandchildren.

To those of us who remember Dr. Angell at his regular attendance at the meetings of the American Neurological Association, he was a soft-spoken, kindly gentleman of the old school. Formerly we saw him regularly at the annual meetings, but of recent years, as his health failed, we saw less of him.

Book Reviews

Penicillin in Neurology. By A. Earl Walker, M.D., Associate Professor of Neurological Surgery, the University of Chicago, and Herbert C. Johnson, M.D., Resident Neurological Surgeon, the University of Chicago. Price \$5. Pp. 202, with 26 tables and 95 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

By presenting the results of their animal and human experimental work on penicillin and integrating their material with the many reports flooding the periodicals in this active and fruitful field, the authors have produced a most useful monograph for all who would utilize penicillin therapy understandingly.

After briefly discussing antibiotics and factors influencing their effective action, the authors present their technic for culturing the offending organism and determining its sensitivity to penicillin, stressing the necessity of this knowledge for proper management. Then are described the experiments which demonstrate the failure of penicillin systemically administered to penetrate the hematoencephalic barrier in the normal brain, while proving its passage in the presence of meningitis. The spinal fluid levels attainable with systemic administration are measured and compared with the concentration needed for therapeutic effect. Since the attainable levels frequently do not suffice, the complemental use of intrathecal, intracisternal and intraventricular injections, and the indications and dangers thereof, are described. The rationale of these procedures is worked out by studying the dispersion of various concentrations of penicillin throughout the cerebrospinal fluid system and correlating the concentrations with clinicopathologic effects. Employing bioassay and electroencephalographic and neuropathologic studies the authors have been able to show that effective concentrations of penicillin can be safely applied to the brain, but stress that intracisternal and intraventricular injections may be required to put the penicillin where it is needed because intrathecal lumbar injection does not disperse well enough. The convulsant effects of overdosage are demonstrated clinicopathologically and by electroencephalogram.

As surgeons, the authors are keenly alert to the possibility of a loculated, poorly draining abscess being the cause of relapse in pneumococcic meningitis, and urge radical simultaneous therapeutic and diagnostic measures, including ventriculography, to discover any suspected focus, which can then be drained surgically. They recognize the amazing control of neurosurgical infections that penicillin has brought, but emphasize the truism that penicillin therapy is never a substitute for adequate surgical drainage. An original technic using penicillin intrathecally in the management of spina bifida is described. The indications for supplementing penicillin with sulfonamide drugs are adequately noted.

In discussing the role of penicillin in neurosyphilis, the authors cite the literature and, while recognizing the efficiency of penicillin, recommended a combination of penicillin therapy and other standard treatment technics. Experience at Bellevue Hospital indicates that adequate penicillin therapy alone suffices, because of the dramatic and sustained return to inactivity of the spinal fluid (Dattner-Thomas). Elsewhere results in treatment of dementia paralytica and tabes have been better when penicillin is combined with malaria. However, the risk is greater.

Finally, Dr. Walker and Dr. Johnson briefly evaluate the neurotoxicity of streptomycin, streptothricin, actinomycin and clavacin and conclude that only streptomycin is safe to employ effectively, the others causing severe damage to the brain, convulsions and death in therapeutic concentrations. As of May 1946, few reports of the efficiency of streptomycin were available, but early hopes are being borne out that a potent weapon against influenza, Salmonella and Escherichia coli infections, and possibly tuberculosis meningitis, is now available.

The authors, both Army neurosurgeons, have done the internist, the neurologist and the neurosurgeon a service in presenting this practical monograph.

| RATE OF REGENERATION IN HUMAN PERIPHERAL NERVES

Analysis of the Interval Between Injury and Onset of Recovery

SYDNEY SUNDERLAND, M.D., D.Sc.

MELBOURNE, AUSTRALIA

THOUGH valuable information continues to accumulate regarding the reparative process following experimental nerve injuries in lower mammals, the available information relating to repair in human material remains incomplete and is still too meager to enable one to determine whether the experimental results are directly applicable to man.

In the present inquiry an attempt has been made to calculate the rate of regeneration after lesions of human peripheral nerves and to analyze the events that occur in the interval between the injury and the onset of clinical recovery. The importance of this information in regard to the treatment and prognosis of peripheral nerve injuries is self evident. The investigation was commenced at an Australian military hospital in 1940, when it was apparent that large numbers of patients with nerve injuries would again come under observation. All the patients here reported on remained under my care until either (*a*) recovery was complete or sufficiently advanced to warrant the patient's return to service or (*b*) the anticipated period of incapacity rendered such a return unlikely. In the latter event the patient was discharged from the service and transferred to the Department of Repatriation, where the facilities provided have enabled observations to be continued over a period of six years. The examinations throughout were conducted by the same observer, considerably reducing the personal factor introduced by the transferring of patients from clinic to clinic. Investigations relating to the rate of regeneration in individual peripheral nerves and of motor and sensory fibers have already been reported.¹ A general review and a discussion of the problems relating to this aspect of repair are now possible.

From the Department of Anatomy and Histology, University of Melbourne.
Aided by a grant from the National Health and Medical Research Council of Australia.

1. Sunderland, S.: (*a*) Course and Rate of Regeneration of Motor Fibers Following Lesions of the Radial Nerve, *Arch. Neurol. & Psychiat.* **56**:133-157 (Aug.) 1946; (*b*) Rate of Regeneration of Motor Fibers in the Ulnar and Sciatic Nerves, *ibid.* **58**:7-13 (July) 1947; (*c*) Rate of Regeneration of Sensory Nerve Fibers, *ibid.* **58**:1-6 (July) 1947.

TERMINOLOGY AND TREATMENT

Latent Period.—The interval between the injury and the onset of clinical recovery is termed the latent period.

Initial Delay.—The interval between the injury and the time when functionally mature fibers appear in the distal segment is termed the initial, or scar, delay, though others² have defined it as the latent period.

Period of Growth and Maturation.—This is the time taken (*a*) by regenerating axons to descend along the distal segment and to reach muscle or skin and (*b*) for the changes to take place which convert the axon into a functionally mature nerve fiber.

Terminal Delay.—This is the time required for the intramuscular and intradermal changes which permit a motor response to voluntary effort and the correct interpretation of a peripheral stimulus. This implies the reestablishment of functional end organ relationships in sufficient numbers and in the appropriate patterns for functional recovery.

Infection and Scarring.—In order to evaluate the influence of these factors on the course of regeneration, an attempt was made in each case to assess the degree of infection and local scarring about the nerve. This was difficult, and only the simplest classification into "significant" and "insignificant" was attempted. The degree of infection was assessed on the basis of general symptoms, culture of material from the wound, the presence or absence of osteomyelitis, the period during which the wound discharged, the time taken for the wound to heal and the extent of the residual scarring. The degree of scarring was estimated on the extent of the injury to soft tissue, the area and density of the residual scar and whether this was adherent, free, depressed or otherwise.

Motor Recovery.—The criteria adopted for ascertaining the return of function were: (*a*) palpable contraction of a muscle or (*b*) movement which was undoubtedly attributable to action of the muscle alone. Due regard was paid to the possibility of transmitted contraction and trick movements. In order to detect the earliest signs of recovery, patients were examined at weekly intervals until all muscles were contracting; from then on the examinations were conducted at monthly intervals, then every three months and finally every six months. When weekly examinations were not possible, and the first appearance of recovery could therefore not be attributed to a specific week, two dates were supplied: (*a*) the last date when the muscle was known to be still paralyzed and (*b*) the date when recovery was first detected.

2. (*a*) Gutmann, E.; Guttmann, L.; Medawar, P. B., and Young, J. Z.: The Rate of Regeneration of Nerve, *J. Exper. Biol.* **19**:14-44 (May) 1942. (*b*) Seddon, H. J.; Medawar, P. B., and Smith, H.: Rate of Regeneration of Peripheral Nerves in Man, *J. Physiol.* **102**:191-215 (Sept. 30) 1943.

Treatment.—Treatment in all cases consisted of daily massage, heat therapy, exercises and supervised and controlled splinting. Electrotherapy was not employed. All muscles were splinted in a position of rest (just sufficient to remove tension) until contraction appeared. These points are mentioned because evidence has been obtained from this study that rest of paralyzed muscles hastens recovery and stretch delays it, while there is evidence to suggest that electrotherapy accelerates the recovery of muscle weight and strength without, apparently, affecting the time of onset of recovery.³ Therefore, since therapy appears to have a certain effect on the onset and progress of recovery, the treatment should be described in any study of rates of regeneration.

PRELIMINARY ANATOMIC INVESTIGATION

For a detailed study of the regeneration which follows injury to any peripheral nerve, a precise knowledge of its anatomy is essential. For this reason, information was obtained on the following points through a dissection of 20 specimens each of the radial, median, ulnar and sciatic nerves: (1) the order and site of origin of individual motor branches measured from selected points on the nerve; (2) the average shortest and longest distances to individual muscles, together with the range of variation of these distances, measured from a selected point directly along the nerve and its branches. The distal point was that at which the nerve entered the muscle; this is mentioned because branches may, after joining a muscle, continue along its surface for some distance before entering it.

The nerves and their branches were dissected throughout their entire course. The measurements, to the nearest millimeter, were then made, in situ, directly along the nerve and its primary and succeeding branches. The presence of multiple branches to muscles made it necessary to study all distances to individual muscles; the shortest and longest distances were obtained regardless of the order in which the branches left the nerve. For the detailed results of this preliminary anatomic investigation, the reader is referred to a series of papers deal-

3. Fischer, E.: The Effect of Faradic and Galvanic Stimulation upon the Course of Atrophy in Denervated Skeletal Muscles, *Am. J. Physiol.* **127**:605-619 (Nov.) 1939. Hines, H. M.: Effects of Immobilization and Activity on Neuromuscular Regeneration, *J. A. M. A.* **120**:515-517 (Oct. 17) 1942. Gutmann, E., and Guttmann, L.: Effect of Electrotherapy on Denervated Muscles in Rabbits, *Lancet* **1**:169-170 (Feb. 7) 1942. Hines, H. M., and Lazerc, B.: Physiologic Basis for Treatment of Paralyzed Muscle, *Arch. Phys. Therapy* **24**:69-73 (Feb.) 1943. Gutmann, E., and Guttmann, L.: The Effect of Galvanic Exercise on Denervated and Re-Innervated Muscles in the Rabbit, *J. Neurol., Neurosurg. & Psychiat.* **7**:7-17 (Jan.-April) 1944. Jackson, E. C. S., and Seddon, H. J.: Influence of Galvanic Stimulation on Muscle Atrophy Resulting from Denervation, *Brit. M. J.* **2**:485-486 (Oct. 13) 1945. Jackson, S.: The Role of Galvanism in the Treatment of Denervated Voluntary Muscle in Man, *Brain* **68**:300-330 (Dec.) 1945.

ing with the metrical and nonmetrical features of the motor branches of human peripheral nerves.⁴ The average shortest distances from certain points to individual muscles, together with their standard deviations, are given in table 1. From the data, the distance from the site of a nerve lesion to the muscles can be estimated provided that the distance of the lesion from the same points is known.

Linell⁵ measured, from fixed points, the level at which branches proceeded from the nerves of the arm and entered their respective muscles (his investigation was incomplete in that the nerve supply to some muscles was not studied). He pointed out, however, that his values referred only to horizontal levels, so that a measurement would not represent the actual length of a branch if it did not pass vertically down the limb. Since most branches do not pursue such a vertical course, his figures cannot be accepted as more than approximations of the length of these nerves. Again, Linell appears to have disregarded the fact that muscles may be supplied by multiple branches and that the branches to individual muscles may arise at widely spaced intervals. This is of importance in that the first branch to a muscle does not necessarily contain the shortest fibers to it.

Seddon, Medawar and Smith^{2b} used Linell's figures in a study of the rates of regeneration in human peripheral nerves. They also employed a hitherto unpublished series of measurements by Feinstein and Highet, of which details have not been provided, though it appears that Linell's methods were closely followed. In the two sets of figures included in their paper, a single value was given for the distance to each muscle. No reference was made to the range of variations in the distance to any one muscle, which is a factor of considerable importance in calculating rates of regeneration and in appreciating certain departures from what is regarded as the normal serial order of innervation.

Thus, in the case of the ulnar nerve, the length of the section between the hypothenar group of muscles and the first dorsal interosseous muscle was calculated by measuring the distances to each muscle from the same point on the nerve trunk and then subtracting the shorter from the longer distance. Feinstein and Highet gave a value of 30 mm. for this

4. Sunderland, S.: The Metrical and Non-Metrical Features of the Muscular Branches of the Radial Nerve, *J. Comp. Neurol.* **85**:93-111 (Aug.) 1946. Sunderland, S., and Hughes, E. S. R.: The Metrical and Non-Metrical Features of the Muscular Branches of the Ulnar Nerve, *ibid.* **85**:113-125 (Aug.) 1946. Sunderland, S., and Ray, L. J.: The Metrical and Non-Metrical Features of the Muscular Branches of the Median Nerve, *ibid.* **85**:191-203 (Oct.) 1946. Sunderland, S., and Hughes, E. S. R.: The Metrical and Non-Metrical Features of the Muscular Branches of the Sciatic Nerve and Its Medial and Lateral Popliteal Divisions, *ibid.* **85**:205-222 (Oct.) 1946.

5. Linell, E. A.: The Distribution of Nerves in the Upper Limb, with Reference to Variabilities and Their Clinical Significance, *J. Anat.* **55**:79-112, 1921.

TABLE 1.—*Shortest Distances to Muscles (in Millimeters)*

Muscle	Taken (1) 10 Cm. Above L. H. E. (Radial) and M. H. E. (Ulnar and Median Nerves); (2) 5 Cm. Above L. T. T. (Thigh Muscles); (3) 5 Cm. Above M. F. E. (Calf Muscles and Popliteus), and (4) at M. F. E. (Rest)*		Taken from Level of Styloid Process of Radius	
	Mean	Standard Deviation	Mean	Standard Deviation
Radial nerve †				
B. R.	82	15
E. O. R. L.	105	11
E. C. R. B.	147	19
E. D. C.	202	21
E. C. U.	202	20
E. D. Q.	217	25
A. P. L.	214	21
E. P. L.	239	23
E. P. B.	259	30
E. I. P.	269	30
Ulnar nerve ‡				
F. C. U.	133	10
F. D. P.	160	13
A. M. D.	33	13
F. M. D.	42	12
O. M. D.	44	12
Hypothenar §....	32	11
L. 4.	56	11
L. 3.	61	13
L. 2.	71	10
L. 1.	82	9
L. 4.	75	10
L. 3.	75	12
A. O.	75	10
A. T.	77	11
Median nerve				
P. T.	129	12
F. C. R.	159	12
F. D. S.	154	12
F. D. P.	193	21
F. P. L.	200	32
F. Q.	293	34
Thenar	55	13
L. 1.	69	12
L. 2.	74	12
Sciatic nerve ¶				
L. B.	161	40		
S. B.	271	35		
S. T.	124	23		
S. M.	246	30		
A. M.	212	34		
M. G.	82	11		
L. G.	90	18		
G. §	81	12		
S.	131	20		
P.	131	16		
T. P.	106	26		
F. D. L.	174	30		
F. H. L.	215	36		
P. L.	94	23		
P. B.	196	32		
T. A.	103	11		
E. D. L.	102	20		
E. H. L.	181	29		
Pt.	257	26		

* L. H. E. and M. H. E. indicate, respectively, the lateral and medial humeral epicondyle; M. F. E. indicates the medial femoral epicondyle and L. T., the ischial tuberosity.

† For the radial nerve, B. R. denotes brachioradialis; E. O. R. L., extensor carpi radialis longus; E. C. R. B., extensor carpi radialis brevis; E. D. C., extensor digitorum communis; E. C. U., extensor carpi ulnaris; E. D. Q., extensor digiti quinti proprius; A. P. L., abductor pollicis longus; E. P. L., extensor pollicis longus; E. P. B., extensor pollicis brevis; E. I. P., extensor indicis proprius.

‡ For the ulnar nerve, F. C. U. denotes flexor carpi ulnaris; F. D. P., flexor digitorum profundus; A. M. D., abductor minimi digiti; F. M. D., flexor minimi digiti; O. M. D., opponens minimi digiti; L., interosseous (1-4); L., lumbricallis; A. O., adductor pollicis, oblique head; A. T., adductor pollicis, transverse head.

§ Shortest distance to the hypothenar group and to the gastrocnemius muscle, regardless of the particular portion of the muscle supplied.

|| For the median nerve, P. T. denotes pronator teres; F. C. R., flexor carpi radialis; F. D. S., flexor digitorum sublimis; F. D. P., flexor digitorum profundus; F. P. L., flexor pollicis longus; P. Q., pronator quadratus; L., lumbricallis.

¶ For the sciatic nerve, L. B. denotes long head of biceps; S. B., short head of biceps; S. T., semitendinosus; S. M., semimembranosus; A. M., adductor magnus; M. G., medial head of gastrocnemius; L. G., lateral head of gastrocnemius; G., gastrocnemius; S., soleus; P., plantaris; T. P., tibialis posterior; F. D. L., flexor digitorum longus; F. H. L., flexor hallucis longus; P. L., peroneus longus; P. B., peroneus brevis; T. A., tibialis anterior; E. D. L., extensor digitorum longus; E. H. L., extensor hallucis longus; Pt. peroneus tertius.

length; the value reported by me was 49 ± 12 mm., and my observations show that their figure is too low for all but the exceptional person. The measurements of Linell and of Feinstein and Highet give the impression, too, that the serial order of innervation of muscles is a constant one, whereas, on the contrary, it is subject to considerable variation. It does not seem to have been appreciated that these variations are an important cause of departures from what is regarded as the normal rate and order of recovery. For example, Stopford⁶ recorded in some cases of lesions of the radial nerve that the extensor carpi ulnaris recovered before the extensor digitorum communis. Seddon, Medawar and Smith, having failed to confirm Stopford's observation, erroneously concluded, owing to the unreliable anatomic data at their disposal, that the earlier recovery of the extensor carpi ulnaris could not be expected on anatomic grounds. I have confirmed Stopford's observation, however, on several occasions, and it was supported by my anatomic investigation. Thus, in 7 specimens the distance to the extensor carpi ulnaris was less than that to the extensor digitorum communis, though in 2 specimens the difference was insignificant; in 11 specimens the distance to the extensor digitorum communis was less, but only significantly so in 4 specimens. In the remaining 2 specimens the figures for the two muscles were the same.

CLINICAL MATERIAL

Clinical observations, which form the basis of the discussion to follow, were made on a series of 301 patients, presenting 339 peripheral nerve injuries, who have been under continuous observation for periods ranging from one to six years. Case histories containing details of the injury and progress of recovery will be reported separately. The data relevant to the present inquiry are contained in tables 2, 3, 4 and 5, in which details are given relating to the following factors: (*a*) cause of the nerve injury and its level; (*b*) presence or absence of significant scarring and infection at the site of injury; (*c*) onset of recovery in muscles supplied by the radial, ulnar and sciatic nerves, and (*d*) advance of Tinel's sign. Additional data will be introduced in the appropriate sections of the text.

REVIEW OF METHODS PREVIOUSLY EMPLOYED TO CALCULATE THE RATE OF REGENERATION

Methods employed for calculating the rate of regeneration have one feature in common—they all measure the rate for a number of fibers in the nerve trunk, and not the rate for a single fiber.

6. Stopford, J. S. B.: The Results of Secondary Suture of Peripheral Nerves, *Brain* 43:1-25 (May 20) 1920.

TABLE 2.—Data Relating to the Lesions of the Radial Nerve

Causative Injury; Nature of Nerve Lesion; Case No.	Level of Lesion Above L. H. E., Cm.	Interval Between Injury and Suture, Days	Wound Infection	Scarring	Return of Voluntary Contraction, Weeks *					
					BR.	E. C. R. L.	E. D. C.	E. C. U.	A. P. L.	E. P. L.
Axonotmesis										
Simple fracture of humerus.										
Case 77.....	10.0	..	Nil	Nil	16	18	23	23	25	27
161.....	10.0	..	Nil	Nil	13	14	21	23	25	28
317.....	10.0	..	Nil	Nil	10	18	24	22	25	29
Gunshot wound										
Case 185.....	12.0	..	Nil	Nil	14	16	22	24	26	30
203.....	9.0	..	Nil	Nil	20	20	27	27	31	31
255.....	2.0	..	I †	S †	8	8	18	18	20	26
264.....	1.0	..	Nil	S	Intact	14	23	23	25	34
Gunshot wound + fracture of humerus										
Case 100.....	7.5	..	I	S	Intact	23	28-31	28-31	32-36	32-36
104.....	5.0	..	I	S	17	20	27	30	31	36
118.....	9.0	..	I	S	16	17-20	17-20	17-20	28	28
231.....	12.5	..	I	S	40	42	50	45	50	56
258.....	5.0	..	I	S	18	22	32	31	35	37
Suture										
Laceration										
Case 180.....	4.0	38	Nil	S	28	20	31	31	34	42
292.....	12.5	Immediate	Nil	Nil	22	27	37	36	40	45
Gunshot wound										
Case 40.....	5.0	313	I	S	Intact	20	34	35	40	40

* BR. indicates brachioradialis; E. C. R. L., extensor carpi radialis longus; E. D. C., extensor digitorum communis; E. C. U., extensor carpi ulnaris; A. P. L., abductor pollicis longus; E. P. L., extensor pollicis longus; L. H. E., lateral epicondyle of the humerus.
† I and S denote significant infection and scarring, respectively.

* BR. Indicates brachioradialis; E. C. R. L., extensor carpi radialis longus; E. D. C., extensor digitorum communis; E. C. U., extensor carpi ulnaris; A. P. L., abductor pollicis longus; E. P. L., extensor pollicis longus; L. H. E., lateral epicondyle of the humerus.
+ I and S denote significant infection and scarring, respectively.

TABLE 3.—Data Relating to the Lesions of the Ulnar Nerve

Causative Injury; Nature of Nerve Lesion; Case No.	Level of Injury, Cm.*	M. H. E. to R. S. L., Cm.*	Interval Between Injury and Suture, Days	Wound Infection	Scarring	Return of Voluntary Contraction, Weeks †		
						F. C. U.	H.	D.1
Axonotmesis								
Laceration								
Case 103.....	5.0 above R. S. L.	I †	S †	..	20	32
Case 323.....	2.0 below R. S. L.	Nil	Nil	..	8	20
Gunshot wound								
Case 30.....	20.0 above R. S. L.	Nil	Nil	..	62	79
31.....	10.0 above M. H. E.	28.0	...	Nil	Nil	27	80	91
129.....	6.0 above M. H. E.	28.0	...	Nil	Nil	4.33	90	107
130.....	17.0 above M. H. E.	29.0	...	Nil	Nil	15	29	41
179.....	8.0 above M. H. E.	27.0	...	Nil	Nil	1.20	22	30
237.....	8.0 above R. S. L.	Nil	Nil	..	34	42
Gunshot wound + bone injury								
Case 43.....	13.0 above R. S. L.	I	S	..	53	61
176.....	14.0 above R. S. L.	Nil	Nil	..	32	39
235.....	1.0 above R. S. L.	Nil	Nil	..	29	40
Suture								
Compound fracture of radius and ulna.								
Case 328.....	15.0 above R. S. L.	29.5	177	Nil	Nil	..	32	42
Laceration								
Case 105.....	25.0 above R. S. L.	30.0	2	Nil	Nil	..	40	65
139.....	1.0 above R. S. L.	Immediate	Nil	S	..	28	51
158.....	2.5 above M. H. E.	27.5	104	Nil	S	18	35	109
269.....	20.5 above R. S. L.	29.0	277	Nil	Nil	..	46	62
290.....	At M. H. E.	25.0	1	Nil	Nil	17	81	102
325.....	8.0 above R. S. L.	5	Nil	S	..	40	54
Gunshot wound								
Case 33.....	8.0 above R. S. L.	191	I	S	..	17	47
Case 183.....	7.0 above M. H. E.	26.0	272	Nil	Nil	28	63	Entirely by median
207.....	6.0 above M. H. E.	26.0	131	Nil	S	14	67	81
277.....	14.0 above M. H. E.	35.0	314	I	S	26	61	Partly by median
Gunshot wound + bone injury								
Case 100.....	6.0 above M. H. E.	26.5	350	I	S	30	67	92-128
243.....	9.0 above M. H. E.	26.5	Immediate	I	S	4.20	37	55
240.....	16.0 above M. H. E.	29.0	1,012	I	S	27	68	No recovery at 100 weeks

* R. S. L. and M. H. E. indicate levels of styloid process of the radius and medial epicondyle of the humerus, respectively.

† F. C. U. indicates flexor carpi ulnaris; H., hypothenar muscles; D.1, first dorsal interosseous muscle.

‡ I and S indicate significant infection and scarring, respectively.

EXPERIMENTAL METHODS

Gutmann, Guttman, Medawar and Young.^{2a}—Five methods were employed by these investigators to measure the rate of advance of axon tips and to follow the process of maturation in the sciatic nerve of the rabbit (*a*) after cutting and suture and (*b*) after crushing. These will be discussed in the order in which they were described. It is to be noted that these authors used the term "latent period" to define the period which in this paper is called the "initial delay." In discussing their observations, the term "initial delay" has been substituted, except in quotations, for "latent period."

First Method: After crushing or division and suture, the nerves were reexposed at various times (usually after fifteen or twenty-five days), and the distance to which regenerating axon tips had advanced was ascertained by pinching the nerve from below upward until a level was reached at which reflex responses were obtained. The presence of axon tips at this level was confirmed histologically, and the tests were so designed as to exclude the possibility of axons coming from any source other than the central stump. The distances were then plotted against times, and, on the basis of the graph thereby constructed, the authors stated:

It appears that after an initial delay in the scar the fibres advance down the nerve at a constant rate. In fact the points of Fig. 1 may reasonably be fitted by a straight line. However, since, in order to facilitate statistical comparisons, nearly all of the observations were made after either 15 or 25 days, it is not possible, from these data, to test the hypothesis that the rate of growth is constant; in all the following calculations it has been assumed to be so.

In an investigation designed to reveal the rate of regeneration, it seems premature to begin with the assumption that the rate was a constant one, and it is not unreasonable to suggest that steps should have been taken at the outset to settle this important question by making use of greater variations in the interval after interrupting conduction in the nerve.

The rate of regeneration and the initial delay, calculated by this method were, respectively, as follows: after crushing, 4.36 ± 0.24 mm. per day and 5.23 days; and after suture, 3.45 ± 0.16 mm. per day and 7.27 days.

On their graph, each point represented data provided from a single specimen, in which at least two variables were operating: (*a*) the duration of the initial delay and (*b*) the rate of advance of the axon tips (even if it is admitted, for the moment, that this remained constant for any individual specimen). Owing to the unavoidable conditions of the experiments, it was not possible for one nerve in the same specimen to provide two points on the graph.

TABLE 4.—Data Relating to Lesions of Sciatic, Medial, Popliteal and External Popliteal Nerves

Causative Injury; Nature of Nerve Lesion; Case No.	Level of Injury, Cm.	Wound Infection	Scarring	Return of Voluntary Contraction, Weeks *					
				G.	F. D. L.	F. H. L.	T. A.	P. I.	E. H. L.
Compression									
Case 188.....	Neck of fibula	21	21	36
215 (right leg).....	Neck of fibula	24	20	36
215 (left leg).....	Neck of fibula	18	18	30
Simple fracture of femur -									
Case 326.....	10.0 above M. F. E.†	29	46	53	43	41-48	49
Gunshot wound									
Case 82.....	Head of fibula	I †	S †	18	18	35
88.....	Lower third of thigh	NH	NH	102	111	111
95.....	5.0 above M. F. E.	I	S	15	24	29	24	10	33
109.....	7.0 above M. F. E.	NH	NH	13	21	21	13	13	21
112.....	23.0 above M. F. E.	NH	NH	26	33	41	28	28	33
145.....	16.0 above M. F. E.	NH	NH	18	37	42	27	27	36
190.....	At M. F. E.	NH	NH	22	42	42
240.....	15.0 above M. F. E.	NH	NH	37	31	44
254.....	Head of fibula	NH	NH	7	7	12
Gunshot wound + bone injury									
Case 150.....	Mid thigh	I	S	13	13	21
260.....	5.0 above M. F. E.	NH	NH	12	35	35
293.....	Mid thigh	I	S	71	59	80

* G. Indicates gastrocnemius; F. D. L., flexor digitorum longus; F. H. L., flexor hallucis longus; T. A., tibialis anterior; P. I., peroneus longus; E. H. L., extensor hallucis longus.
† F. F. E. means medial epicondyle of the femur.
‡ I and S denote significant infection and scarring, respectively.

On this graph, the initial, or scar, delay was calculated "as the point at which the regression line of distance traveled by the new fibers on time cuts the base-line," for calculation of which it was necessary to assume that the rate of growth was constant and the line representing it a straight one. The authors admitted that this period was not carefully determined by independent experiments. Such a calculation of the initial delay does not justify the acceptance of this figure as a constant for all specimens, nor does it seem expedient to make use of the calculation in determining the rate of growth in individual specimens. Thus, the equation

$$R = \frac{D}{T-I}$$

where R is the rate of growth; D , the distance covered by fibers; T , the duration of the experiment, and I , the initial delay, gives the rate for any specimen only if the duration of the initial delay is accurately known for that particular specimen. When values calculated from a large series of specimens (one reading only per specimen) are plotted on a graph, the growth line, whether it is straight or curved, can provide only a mean value for the initial delay and a mean value for the rate of regeneration for all the specimens contributing to its construction; from such a graph it is not possible in any particular specimen to estimate either the initial delay or the rate.

The initial delay is of particular significance in the interpretation of the data provided by each experiment. Variations in its duration are to be expected (which will influence the distance traveled by regenerating fibers down the peripheral stump in a given time), especially when the lesion is one of division and suture; it is more likely to be constant when the basis of the injury is constant (as in crushing). The following references demonstrate that the authors were aware of variations in the duration of this period:

. . . among the rabbits examined 15 days after plasma suture of the tibial or peroneal nerves, distances of outgrowth ranging from 23 to 38 mm. were recorded, with a mean of 30.1 and standard deviation of 5.3. This scatter is greater than would be expected from phenotypic and genotypic differences alone, but perhaps not more than might be expected from differences in the making of the suture [page 18].

. . . Presumably the period will vary considerably with the closeness of apposition of the stumps when the suture is made, and a large part of the variation in the distances of outgrowth recorded must be due to this cause. Indeed, it is possible to some extent to forecast from observation of the closeness of apposition at operation, whether the distance reached will be large or small. For instance, in rabbit 191 it was recorded at operation that whereas the apposition on the right side was "excellent" that on the left was "rather less successful." After 15 days it proved that fibers had reached to 38 mm. on the right but only 33 mm. on the left. Histological examinations confirmed that the union was closer on the right.

TABLE 5.—*Details Relating to Advance of Tinel's Sign and Rate of Regeneration Calculated Therefrom*

Nerve; Nature of Nerve Lesion; Case No.	Level of Lesion, Cm.*	Date of Exami- nation After Injury, Days	Level of Tinel's Sign Below Lesion, Cm.	Distance Traveled by Axons, Mm.	Time, Days	Rate of Regen- eration, Mm./Day
Median						
Suture						
Case 322.....	16.0 above M. H. E.	218	180			
				90	54	1.7
		272	270	85	114	0.7
		386	355	15	19	0.8
		405	370	60	100	0.6
		505	430			
Ulnar						
Lesion in continuity						
Case 24.....	At M. H. E.	39	100			
				170	111	1.5
		150	270			
Suture						
Case 105.....	25.0 above R. S. L. }	71	150			
	5.0 below M. H. E. }	112	250	100	41	2.4
Case 127.....	At M. H. E.	105	190			
		168	270	80	63	1.3
Case 182.....	At M. H. E.	46	130			
		109	250	120	63	1.9
Case 290.....	At M. H. E.	33	15			
		71	110	95	38	2.5
		163	290	180	92	2.0
		199	320	30	56	0.8
Case 322.....	16.0 above M. H. E.	113	200			
		167	285	85	54	1.6
		281	355	70	114	0.6
		300	370	15	19	0.8
		400	420	50	100	0.5
Sciatic						
Lesion in continuity						
Case 270.....	Mid thigh	258	100 †			
		382	300 †	200	124	1.6
		498	340 †	40	116	0.3
Suture						
Case 94.....	20.0 above M. F. E.	108	280			
		206	440	160	98	1.6
		248	490	50	42	1.2
		290	520	30	42	0.7
		512	630	110	222	0.5
Case 122.....	36.0 above M. F. E.	129	280			
		250	540	260	121	2.1
		320	640	100	70	1.4
Case 137.....	2.0 above M. F. E.	140	300			
		306	570	270	166	1.6
External popliteal						
Lesion in continuity						
Case 174.....	Neck of fibula	337	150			
		435	220	70	98	0.7

* M. H. E. and R. S. L. denote medial epicondyle of humerus and level of styloid process of radius, respectively.
† Measurements taken from the head of the fibula.

Referring to the results following suture of the sciatic nerve in the dog, they stated:

The delay in the scar cannot have been less than 8 days, and may have been more, since the junction was not a very satisfactory one, so the rate of growth of the fibers must have been at least 2.3 mm./day.

In any case we may conclude that, as with sensory fibers, the rate is lower, and the latent period longer, after cutting and suturing the nerve than after interruption by crushing.

Elsewhere, however, the initial delay was regarded as a constant. Thus, referring to the scatter in the estimates for distances, they concluded that "it is individual differences in the rate of regeneration rather than in the latent period that is responsible for the scatter of the estimates." Again, they stated that, after crushing, "the distances reached are considerably greater than those which would have been found after complete severance and suture of the nerve, although, as already mentioned, the latent period is hardly different in the two cases. In fact, the greater distances reached after the operation of crushing are due to the faster growth of fibers in the peripheral stump."

In view of these conflicting statements, it is difficult to ascertain the precise views of the authors on the initial delay. It would appear, however, that both the initial delay and the rate of growth show individual variations.

Second Method: The peroneal nerve in the rabbit was crushed at various levels in different specimens. The distance from the lesion to the lowest point of the analgesic area of the foot, together with the time taken for pain sensibility to reappear at this point (as indicated by the ability to elicit reflex responses by the application of painful stimuli), was recorded for each lesion.

From these data a graph was constructed, from which a rate of growth of 3.04 ± 0.35 mm. per day and an initial delay of 9.8 days were calculated. As already pointed out, data treated in this way can provide only mean values for the rate and the initial delay, and these should not be used for calculating values in individual specimens. This point is further illustrated by a separate account of the results in 4 of the experiments, in which the nerves were crushed at different levels on the two sides of the same animal. The rates ranged from 3.03 to 3.95 mm. per day, with a mean of 3.39 mm., and the initial delay varied from 12.7 to 29.2 days, with a mean of 19.0 days. Thus, even with a crush injury, in which the lesions might reasonably be expected to be comparable over a series of animals, the initial delay varied from 12.7 to 29.2 days. It would seem futile, therefore, to postulate a constant initial delay in calculating the rate in any one case.

The rate was slower in the experiments devoted to a recording of recovering sensation. To explain this, it was suggested that the rate of advance of maturation was being measured. There is, however, no

evidence that this was the case. On the application of a painful stimulus to the skin, the presence of immature fibers is sufficient to provide the basis for reflex activity. A similar response follows both pinching the exposed nerve and application of a painful stimulus to the cutaneous area, and the impulses in both experiments could be transmitted by fibers showing similar morphologic features; in one set of experiments the impulses were shown to arise in bare axon tips. A significant difference in the two experiments, however, was that effects of pinching the nerve were recorded within twenty-five days, while pricking the skin did not elicit a response until from sixty-seven to one hundred and one days after the nerve was crushed, by which time the fibers had covered much greater distances. Furthermore, the reinnervation of skin involves additional and complicated changes in the superficial cutaneous plexuses.

As an alternative explanation of the slower rate, it could be argued that since the distances to be covered were much greater and the duration of the experiments was longer the rate in the later stages may have slowed down, thereby resulting in a slower average rate for the duration of the experiment and the distance over which it was measured. The suggestion of a progressively diminishing rate as recovery proceeds is, of course, in conflict with the basic assumption of the authors that the rate is constant.

Third Method: The rate was measured at which a denervated cutaneous area diminished during the reappearance of pain sensibility which was sufficiently intense to elicit reflex responses; the possibility of overlap from adjacent cutaneous nerves was excluded.

Gutmann and his associates regarded this process as an example of the "advance of functional completion of sensory nerve fibers"; they failed to exclude the possibility, however, that the presence of immature fibers may be sufficient to permit the elicitation in the animal of those responses which are thought to signify sensory recovery. The rate of shrinkage was 2.05 ± 0.14 mm. per day after crushing and 1.57 ± 0.15 mm. per day after suture. Presumably, the range over which the rate varied was again calculated on the basis of a constant initial delay.

To account for the low rate, two explanations were offered: (1) the distance between two points on the surface of the skin does not represent the whole of the distance that the nerve fibers must travel before the advancing edge of sensitivity moves from one point to another; (2) the regenerative processes may proceed more slowly in the ultimate plexus than in the main nerve trunk.

Fourth Method: The peroneal nerve was crushed, or severed and sutured, at various levels in different specimens and the time recorded at which motor recovery made its first appearance. The criterion of returning motor function was the reflex spreading of the toes which

occurs on suddenly lowering an animal held by "the scruff of the neck." The distances from the lesions to the muscles responsible were obtained by direct measurement along the nerve, though the distal end point was not given. In this test, it is the recovery of muscles to a stage at which they are able to participate in reflex activity that is being examined. Though it was claimed that reflex activity of this type is an indicator of conduction which is dependent on the matured fiber, there is no convincing evidence that such activity demands a degree of maturation commensurate with that required for the restoration of functionally effective voluntary activity.

A graph was constructed from the observed times and distances, and from these data were calculated a rate of growth of 3.05 ± 0.14 mm. per day and an initial delay of 20.8 days. The error of using a mean value for the initial delay in calculating the rate in an individual specimen has already been pointed out; it is further illustrated by the results in 4 specimens in which the nerve had been crushed high on one side and low on the other. The rates ranged from 2.86 to 3.29 mm. per day, with a mean of 3.1 mm.; and the initial delay varied from 20.41 to 22.52 days, with a mean of 21.6 days. Another series of experiments, in which the nerves were severed and joined with plasma, gave a rate of 2.02 ± 0.3 mm. per day and an initial delay of 32.3 days. In 4 animals the nerve was cut and joined high on one side and low on the other. The rates ranged from 2.17 to 2.93 mm. per day, with a mean of 2.6 mm.; and the initial delay varied from 29.8 to 42.5 days, with a mean of 36.5 days.

The slower rate obtained with this method was explained on the supposition that it was the rate of advance of maturation that was under review. The experiments, however, involved longer distances and greater times than those designed to reveal the rate of advance of axon tips, and it is believed that the over-all slower rate is more satisfactorily accounted for by a progressive diminution in the rate with the advance of repair.

In applying this method for estimating rates, it was assumed by the authors that in two given muscles there would be no significant variation in the terminal delay. They designed control experiments in order to detect any possible error in this connection.

In 3 rabbits the nerve was crushed high on one side and low on the other. About the time when it was calculated that regenerating motor fibers from the proximal lesion on one side would have reached the level of the distal lesion on the other, the lower lesion was recreated by crushing the nerve again at the old site. In this way it was hoped to insure that the regenerating fibers from different levels would reach muscles which had been denervated for the same period. A comparison of the results of this set of experiments with the results given

by the experiments in which the nerves were crushed only once led the authors to state that "it is perhaps just suggestive of a prolongation of the period of delay with progressive atrophy of the muscle." Three possible sources of error in the control experiments were considered:

(1) . . . After the second interruption the outgrowth of fibers might be less (or conceivably more) vigorous than after an initial lesion. But in other experiments (Holmes & Young) the outgrowth has been found to be at all times equally vigorous under such conditions. (2) The scar resulting from the first operation might delay the fibers. Other experiments in which high rates of growth have been observed through much more seriously scarred nerves show that this is unlikely. . . . (3) Since the distance between the two lesions was greater than that of the lower one from the muscle it is clear that for a few days before the second operation axon tips must have been present in the muscle on the low-operated side, and might possibly have had some effect on the condition of the muscle fibers.

Other possible sources of error which were not mentioned are:

1. Since it is impossible to forecast accurately the rate and initial delay for any individual specimen, there is a very wide range of variation in the time when the fibers from the proximal lesion would reach the level of the distal lesion; there is, consequently, no assurance that the distal lesion will be renewed at the appropriate time.

2. No account was taken of the initial delay—which may vary greatly—occurring after the second crushing.

3. In the event of the rate of growth not being constant, a further source of error is introduced.

For these three reasons, the control experiments are unlikely to provide the desired information.

Fifth Method: The rate of growth of functionally mature motor fibers was calculated from the distance between two muscles and the interval between the times of their recovery. The times were recorded at which reflex spreading of the toes and dorsiflexion of the foot were elicited by pricking the sole. The distance between the two muscles concerned was not measured in the 6 specimens studied, however, but was obtained from 2 others. This method of testing the return of muscle function again throws doubt on the validity of the assumption that it is the advance of maturation which is being measured.

The estimated rate of advance of "functional ability" was 2.2 mm. per day, while in 1 case of suture the rate of 1.2 mm. per day was recorded. These figures were regarded as "at best a very rough approximation," and the method was dismissed as unsuitable.

Conclusions: This somewhat detailed examination of the experimental investigations of Gutmann and associates^{2a} has been necessary because, despite their comprehensive treatment of the problem and the acknowledged value of their contributions, the investigations fail to

provide entirely satisfactory evidence and raise certain objections of a highly significant nature; there is, however, justification for the claim that the rate following suture is slower than that following crushing. These objections may be stated as follows:

1. Their calculations are based on the assumption, for which there is no justification, that the rate is constant. This is, in itself, a fundamental weakness in an investigation designed to reveal the rate.

2. It is significant that, owing to the unavoidable conditions of the experiments, the distances and times were provided by single observations on each of a number of nerves in a series of rabbits—in only one method (the fifth) could a single nerve provide two readings, and this method was dismissed as unsuitable. For this reason, it was impossible to calculate either the rate or the initial delay in any individual specimen—the most that could be expected of the methods would be a mean rate distributed over all the specimens. From this information it is possible to calculate an average initial delay; but since this period has been shown to vary, it could not be usefully employed for calculating the rates in individual specimens.

3. It would appear that in all their experiments the authors were testing reflex activity. In four of the methods it was claimed that it was the "advance of functional completion" of motor and sensory nerve fibers which was being measured, and that reflex activity of the type employed was an indicator of conduction through a fully matured nerve fiber. There is, however, no convincing evidence either that such activity depends for its expression on a completely matured axonal pathway or that it is not as efficiently served by an immature axon soon after reaching its end organ. As a result, the relationship between the rate of advance of axon tips and that of full maturation remains uncertain.

4. There is ample evidence of a considerable range of variation in the initial delay. Opposed to this is the repeated assumption (on which calculations are based) that this period is constant.

5. The growth of axon tips was studied for shorter times and over shorter distances than was the rate of "advance of functional completion." The difference in rates was attributed to differences in the structure of the conducting fiber. There are, however, cogent reasons for attributing, in part at least, the higher rate in the former to the short duration of the experiments and for believing that in the latter the rate had had time to slow down. This, in turn, implies a progressive diminution in the rate as regeneration advances.

6. Considerable limitations are imposed by animal experimentation with reference to the extension of the observations to clinical neurology.

(a) The distances over which the process can be traced are very short as compared with those in man.

(b) In animals it is not possible to apply tests which depend on voluntary control and on the transmission of sensory impulses which will permit their correct interpretation.

Ramón y Cajal.—Ramón y Cajal⁷ demonstrated "from numerous measurements in rabbits, cats and dogs whose sciatic nerve was completely cut across" that "the velocity of the cones of growth in the peripheral stump is between 2 and 3 mm. in 24 hours. . . . In some really exceptional cases the velocity of growth was 4 mm. per day." Individual data, however, were not given, nor were his methods detailed.

CLINICAL METHODS

The difficulties experienced in accurately estimating rates of recovery in human peripheral nerves are considerable since only a small proportion of a large series of cases will provide the data which are essential for the calculation of the rate. Thus, of 500 cases at the Oxford Centre, Seddon, Medawar and Smith^{2b} found only 33 suitable for this purpose (25 for the study of motor and 4 for the study of sensory recovery, and 4 for calculating the rate of advance of Tinel's sign). In a series of 301 cases, I had 50 nerve injuries (13 of the radial, 21 of the ulnar and 16 of the sciatic nerve) suitable for calculation of the rate of regeneration of motor fibers and only 13 in which the rate of advance of Tinel's sign could be estimated. References to the rate of recovery by other investigators⁸ are not sufficiently detailed to be of value.

Seddon, Medawar and Smith.^{2b}—These investigators employed three methods for calculating the rate.

1. The times of the reappearance of voluntary contraction were charted against the distances from the site of the lesion to the muscles. From the graph thereby constructed they calculated (1) "the rate of advance of the wave front of functional maturation" and (2) the initial delay, which was obtained by projecting the line representing the growth rate so as to intersect the basal line of time.

"In most of our cases," said the authors,^{2b} "the assumption that the rate of recovery is *constant* over the range of times and distances within

7. Ramón y Cajal, S.: *Degeneration and Regeneration of the Nervous System*, London, Oxford University Press, 1928, vol. 1.

8. (a) Tinel, J.: *Nerve Wounds*, London, Baillière, Tindall & Cox, 1917. (b) Dustin, A. P.: *Les lésions post traumatiques des nerfs: Contribution à l'histopathologie du système nerveux périphérique chez l'homme*, Ambulance de l'océan 1 (pt. 2):71-161, 1917. (c) Marble, H. C.; Hamlin, E., Jr., and Watkins, A. L.: *Regeneration in the Ulnar, Median and Radial Nerves*, Am. J. Surg. 55:274-294 (Feb.) 1942.

which the readings lie gives a very satisfactory approximation to the data," although there were "remarkable variations in rate, even for lesions of the same nerve and, if anything, even greater variations in the 'latent periods.'" The results in 7 of these cases were unusual in that the initial delay, as calculated by extrapolation, fell on the negative side of the time axis. To account for this, it was assumed that in the initial stages the rate must have been much greater than that calculated; this, in turn, invalidated the method for obtaining the initial delay, even when this had been shown to have a positive value, and led to a final pronouncement that "there will be no temptation to estimate the latent period by extrapolation." This assumption of a diminishing rate was supported by the findings in 3 cases, from which a curve of growth was obtained. From a detailed mathematical analysis of the findings in these 3 cases, it was inferred that "the rate of regeneration is initially as high as 3 mm. a day, and that it falls off progressively down to and then below a value of the order of 1 mm. a day about 100 days after recovery has started."

These conflicting results were reconciled by suggesting that, though the rate falls off progressively over the whole period of recovery, it may reasonably be assumed to be constant over "moderate ranges of time and distance" at the following average estimates: (1) in the radial nerve: (a) after suture: 1.6 ± 0.2 mm. per day; (b) after axonotmesis: 1.5 ± 0.1 mm. per day; (2) in all nerves studied: (a) after suture: 1.5 ± 0.2 mm. per day; (b) after axonotmesis: 1.4 ± 0.1 mm. per day.

The term "moderate ranges of times and distance" was not qualified, though the diminishing rate was assigned to the phase before "the range of times and distances accessible to measurement" (that is, preceding the onset of recovery) and to the later phases in a few cases in which the regenerative process was spread over a long period. The moderate ranges of distance, therefore, must have been the difference between the measurements to the first and the last muscle innervated, while the range of time would be the period intervening between the reappearance of contraction in the same two muscles. From the included graphs, this period appears to have commenced at about one hundred days and to have extended over the next one hundred to two hundred days. It had previously been inferred from the curved graphs, however, that the rate would fall below the order of 1 mm. per day about one hundred days after recovery had started, and presumably this recovery meant the first reappearance of voluntary contraction. From this it can only be assumed that over "the moderate ranges of times and distance" the rate could not be constant at the average estimates given.

Another error was introduced into the calculations of Seddon, Medawar and Smith by their acceptance of values, in which no account was taken of any variation, for the distances between the bony landmark

and the muscle innervated. The distance to any individual muscle varies greatly in different subjects, but the authors used a constant value, based, it would appear, on an average obtained from a number of cases. In this they were undoubtedly misled by the anatomic data at their disposal. In the construction of their graphs, therefore, the figures on the distance axis are based not on measurement but on assumption, and their possible inaccuracy may explain the negative initial delay obtained in their graphs. Thus, instead of the fibers advancing at a much greater rate in the early stages, it is conceivable that they had shorter distances to cover before innervating the muscles; this could sufficiently depress the growth line to carry its projection onto the positive side of the time axis.

2. The rate of advance of axon tips was calculated on the basis of an advancing Tinel sign. Observations were made on 6 nerves of 4 patients after suture. The rates of recovery varied from 1.37 to 2.25 mm. per day, with an average of 1.71 mm. In 5 of the cases a negative initial delay was obtained by projection of the straight line of growth obtained in the graph. Readings in the earlier stages of recovery would have corrected this, but in one of the graphs (fig. 8) there is sufficient evidence to indicate a falling off of the rate over the period for which the observations were conducted. The data included in this graph, however, were confusing in that a comparison of the fourth and fifth readings for the ulnar nerve and the fifth and sixth readings for the median nerve show a regression, and not a progression, of Tinel's sign. An examination of all the data provided would not support their assumption that the rate, as represented by the growth line in the graphs, is constant.

3. The rate of regeneration was estimated by following the retrogression of the upper margin of an elongated zone of cutaneous sensory loss during recovery. This is the clinical equivalent of the third method employed by Gutmann and associates.^{2a} The recovery of pain and touch sensibility was followed in 4 patients, and the conditions of the investigation were apparently such as to insure that the advance of functional maturity was being measured. Rates varying from 0.78 to 1.28 mm. per day were obtained, with a mean of 1.08 mm. As pointed out by the authors, the cases were not numerous enough to warrant discussion, though they form a guide to the rate at which the completed process advances in the cutaneous plexuses.

*Sunderland.*¹—Two methods were employed to calculate the rate and to ascertain whether or not it was constant and, if not constant, to determine the manner and extent to which it varied.

First Method : After injury of a nerve, with or without suture, the rate of advance of Tinel's sign (which is thought to signify the location of sensory axon tips) was calculated over various segments

of nerves and at different stages of recovery (table 5). After suture, regenerating sensory fibers advanced down the forearm and leg at a progressively diminishing rate, which in the initial stages might be as great as 3 mm. a day for the forearm and 2 mm. for the leg. The rate then slowed until it reached a value of approximately 0.5 mm. per day at the wrist and ankle.

Second Method: With this method, the details of which are provided in an earlier paper,^{1a} the rate of advance of functionally mature motor fibers was calculated over successive segments of a nerve by the use of the formula:

$$R = \frac{L^2 - L^1}{T^2 - T^1}$$

where L^1 and L^2 are the shortest distances to two muscles from a point on the nerve proximal to the site of origin of its first branch. Values for these lengths were provided by preliminary anatomic investigations⁴ (table 1).

T^1 and T^2 signify the duration of the time, in days, between the date of the injury (or suture) and the date of recovery in the two muscles. These values were obtained from clinical observations on patients with peripheral nerve injuries. To qualify for selection, a case had to fulfil the following conditions:

1. Interruption of conduction must be complete and associated with wallerian degeneration.
2. The onset and progress of recovery must be such as to suggest uniform involvement of fibers at the site of injury.
3. The onset and progress of recovery must be such as to suggest that the axons had commenced to regenerate at about the same time.
4. Any departure from the normal order of recovery of muscles should be capable of satisfactory explanation on the basis of established anatomic variations in innervation.
5. In order to detect the earliest signs of recovery in individual muscles, the patients had to be examined at intervals not exceeding a week until all the muscles were contracting.

The accuracy of the formula depends on the following assumptions:

1. That the delay at the site of injury is the same for regenerating axons destined for the two muscles. There can be no certainty of this after suture, but in axonotmesis this factor can be controlled by the careful selection of cases.
2. That the intramuscular distance to be covered before the reestablishment of neuromuscular relations is the same within each muscle. Anatomic investigation has shown that the intramuscular length of the fibers was proportional to the size of the muscles and was approximately the same in muscles of comparable dimensions.

3. That, in the two given muscles, there is no significant difference in the terminal delay. In order to reduce this possible source of error to a minimum, the rate was calculated independently over several short segments of the nerve. This meant that there was no great difference between the length of time for which the two muscles were denervated.

4. That in the same segment of nerve there is no difference in rate between fibers destined for the two muscles and that there is no significant diminution in rate over the additional distance to the more distal muscle. Since the rate normally diminishes as the axons advance, this formula should not be employed when a considerable distance separates the muscles; selection of suitable muscles enables the rate to be calculated over several short sections of the nerve.

The method has the following advantages:

1. It renders unnecessary a knowledge of the level of the injury, since the distance along the nerve to the origin of the proximal branch is common to the measurement for each muscle.

2. It renders unnecessary a knowledge of the initial delay at the site of the lesion. This is especially convenient, since in each individual case the delay cannot be estimated with any degree of accuracy.

3. By selecting muscles innervated at different levels, the rate of regeneration can be estimated over different segments of the nerve. By this means it can be ascertained whether or not regeneration proceeds uniformly during the entire process, though the rate cannot be estimated in the section between the level of injury and the origin of the first branch.

The rate of regeneration can be estimated in any individual case, or an average rate, calculated from the average readings for $T^2 - T^1$, can be obtained from observations on several patients. In an individual case it is necessary to take into consideration the unpredictable range of variation, from subject to subject, in the length of the shortest fibers to any given muscle. When mean readings for $L^2 - L^1$ and $T^2 - T^1$ are obtained from a number of cases (as in the present inquiry), it is believed that this unpredictable element is reduced to a minimum. By taking average values for $L^2 - L^1$ and $T^2 - T^1$, factors are disregarded which are peculiar to an individual subject and which may influence the rate. Regardless of the method employed, however, the rate in any individual case can be calculated only in retrospect—that is, after regeneration itself has rendered available the figures for T^1 and T^2 , and even then the figures for L^1 and L^2 must be average values obtained from the cadaver, for there is no way of obtaining this information in the living subject. For these reasons, an average estimate only has been sought, which, in view of the possible sources of

error, can make no claim to great accuracy. In this connection one was influenced by the warning of the late Wilfred Trotter⁹:

Results: Calculations for the radial, ulnar (in the hand) and sciatic nerves have already been made available.^{1a, b} Seven cases of suture of the ulnar nerve have now accumulated in which it was possible to measure the time taken to travel the length of the forearm (table 3, cases 100, 158, 183, 207, 246, 277 and 290) and, from this information, to calculate the rate for this section of the nerve. The distances involved, however, were greater than those for which the method was designed. Though no great accuracy, therefore, is claimed for the results, they at least provide a guide to the mean rates for the length of the nerve in the forearm, which for the cases, in the order stated, were: 1.0, 0.6, 1.0, 0.7, 1.0, 1.0 and 0.6 mm. per day. Furthermore, the results were such as to justify the conclusion that the rate in the forearm was greater than that in the hand.

For the entire series, the mean rates, in millimeters per day, were as follows:

After axonotmesis

Radial nerve: 1.9 mm. for segments about the elbow
0.8 mm. for segments in the midforearm

Ulnar nerve: 0.6 mm. for the terminal section in the hand

Sciatic nerve: Diminution in rate from 2 to 1 mm. per day over the popliteal divisions in the region of the knee and the upper half of the leg

After suture

Radial nerve: 1.2 mm. for segments about the elbow
0.6 mm. for segments in the midforearm

Ulnar nerve: 0.8 mm. when measured over the entire length of the nerve in the forearm

0.4 mm. for the terminal section in the hand

General Conclusions Based on Personal Observations.—1. The suggestion,¹⁰ based on experimental studies, "that there is not likely to be a decline in the rate of growth of fibers in the distal portions of long nerves, such as those of man" is not supported by the findings in this investigation.

There is, on the other hand, convincing evidence that the rate of advance of both the axon tips and the process of functional maturation diminishes progressively over the whole period of recovery and should not be regarded as constant for any phase of the process. This is not surprising, for a steadily diminishing rate is characteristic of most growth processes.

9. Trotter, W.: *Collected Papers*, London, Oxford University Press, 1941. The affectation of scientific exactitude in circumstances where it has no meaning is perhaps the fallacy of method to which medicine is now most exposed.

10. Young, J. Z.: *The Functional Repair of Nervous Tissue*, *Physiol. Rev.* 22:318-374 (Oct.) 1942.

2. The axon tips advance with a greater velocity than does the process of functional completion.

3. The rate for any particular segment of the nerve depends on its distance from the parent neurons and is not affected by the level of the injury, though the latter is all-important in fixing the initial velocity of regeneration. Thus, the initial rate is faster when the lesion is close to the cell bodies and slower when the lesion is more remote. In the former case, the rate slowly diminishes and, on reaching the more distal level, approximates the commencing rate of regeneration for a lesion in that segment.

4. There is evidence that the rate of regeneration following axonotmesis is greater than that following suture for all sections of the nerve. The difference is greater proximally; over the terminal portion of the nerve the rates appear to approximate. From the data available it is not possible to ascertain precisely the extent to which the rate is slower after suture.

5. After axonotmesis, the rate of advance of functional maturation over the proximal portion of the nerve, in the upper part of the arm and thigh, is probably in the vicinity of 3 mm. per day and slowly diminishes to approximately 0.5 mm. per day over the distal portion, in the hand and foot.

6. After suture, the axon tips advance down the forearm and leg at a rate, in the vicinity of the elbow and knee, of approximately 3 and 2 mm. per day, respectively, but which gradually slows until, at the wrist and ankle, it is commensurate with that observed for functional completion.

7. The observation that the rate is greater after axonotmesis than after suture suggests that there are factors which can influence it.

8. Two factors which greatly influence the result operate in any calculation of the rate: (a) the length of nerve over which the rate is calculated and (b) the level of the segment of the nerve over which the rate is measured.

ADVANCE OF AXON TIPS AND MATURATION OF NERVE FIBERS

After a nerve injury which results in wallerian degeneration, anatomic repair is directed toward (a) reconstituting the axonal pathway between the central stump and the peripheral end organ, and (b) converting the axon into a functionally mature nerve fiber, on which depends its capacity either to conduct an impulse initiated by the cerebral cortex or to transmit sensory impulses which can be correctly interpreted.

Functionally effective repair implies such additional factors as (a) the reestablishment of old relations with the end organs, without distortion and in sufficient numbers to permit the action of fibers in groups large enough to provide for integrated and controlled activity, and (b) subsequent to the reestablishment of simple anatomic continuity, the restoration of the end organ to a state fit for functioning. It is not proposed to consider any local factors at the site of injury which may influence the restoration of the fiber pattern; though the reestablishment of correct relations between the nerve cell and the peripheral end organ depends on these factors, they do not fall within the scope of the present inquiry. In any case, these considerations do not apply in axonotmesis, since in such injuries the fiber pattern is fully preserved.

There is evidence that the restoration of function does not follow immediately on the reestablishment of anatomic continuity between the central stump and the end organ. Thus, electromyographic responses typical of reinnervated muscle can be obtained from paralyzed muscles prior to the reappearance of voluntary contraction.¹¹ This feature is illustrated in 3 cases in my series.

CASE 176.—A. M. T. sustained a perforating gunshot wound of the left forearm on Dec. 27, 1942, which resulted in complete interruption of conduction in the ulnar nerve below the branches to the flexor carpi ulnaris and flexor digitorum profundus muscles. The wounds healed without any complications; a tender swelling developed on the nerve beneath the wound of entry at the level of the mid forearm. The lesion of the ulnar nerve was still complete two hundred and seventeen days after the injury, when the nerve was explored (Major H. Trumble). The small swelling on the ulnar margin of the nerve was only lightly adherent to neighboring structures. Direct stimulation of the nerve above the bulb resulted in slow, wormlike contractions of the hypothenar muscles. The strength of current required to elicit these responses was greater than that required to elicit a similar response from neighboring muscles innervated by the median nerve. In view of this conduction, the wound was closed without disturbing the nerve. Voluntary contractions returned in the hypothenar muscles a week later and in the first dorsal interosseous muscle in seven weeks after that. The patient subsequently made a recovery which was judged just short of normal; residual motor disability was due to injuries to the metacarpal bones received at the time of the original injury.

CASE 231.—J. W. A. sustained a perforating gunshot wound of the right arm on Aug. 24, 1943, resulting in a comminuted fracture of the midthird of the shaft of the humerus. There was extensive injury to soft tissues, and the field notes stated: ". . . the radial nerve was torn and a piece blown away. The proximal end was lying in the wound and terminated at the level of the upper end of the humerus." Fifteen weeks after the injury there was a complete lesion of the nerve involving the brachioradialis muscle and the posterior cutaneous nerve of the forearm. Because of infection, exploration (Major H. Trumble) was delayed until twenty-six weeks after the injury. Local scarring was considerable. The

11. Weddell, G.; Feinstein, B., and Pattie, R. E.: The Electrical Activity of Voluntary Muscle in Man Under Normal and Pathological Conditions, *Brain* 67: 178-257 (Sept.) 1944.

nerve was exposed in the middle and distal thirds of the arm; it had not been severed and was not involved in scar tissue. Electrical stimulation produced weak contraction of the brachioradialis. The strength of current required to elicit this response was greater than that required to elicit a similar response from normal muscle. Since spontaneous regeneration apparently was taking place, the nerve was left undisturbed and the wound closed.

Voluntary contraction did not appear in the brachioradialis until forty weeks after the injury, that is, fourteen weeks after a response had been obtained by electrical stimulation of the nerve. Recovery then proceeded uninterruptedly and in anatomic order until, at the end of fifty-six weeks, all muscles were contracting. The power steadily improved until, at the end of seventy-seven weeks, all movements could be performed against resistance and the power of the grip was one third that on the opposite side. At this stage there had been slight improvement in cutaneous sensation.

CASE 237.—S. C. sustained a perforating gunshot wound of the left forearm on Dec. 8, 1943, which resulted in complete interruption of conduction in the ulnar nerve. A fusiform swelling appeared on the nerve beneath the scar of entry, 8 cm. above the distal crease in the wrist. There appeared to be some recovery of sensation at the base of the hypothenar eminence one hundred and twenty-five days after the injury; there was no further improvement. The nerve was explored by Major H. Trumble one hundred days later. It was observed to enter scar tissue 8 cm. above the distal crease in the wrist and was there bound to the neighboring tissues. Within this scarred zone the nerve was expanded for about 1 inch (2.5 cm.) into a fusiform swelling, which showed a transverse constriction at its middle. Stimulation of the nerve above the bulb gave weak contractions of the intrinsic muscles of the hand and of the ulnar half of the flexor digitorum profundus muscle. Apparently, a branch proceeded to the deep flexor muscle from the scarred segment of the nerve. The strength of current required to elicit these responses was greater than that required to elicit a similar response from neighboring muscle innervated by the median nerve. The wound was closed without freeing the neuroma.

Thirteen days later feeble voluntary contractions were first observed in the hypothenar muscles—an additional eight weeks elapsed before contractions appeared in the first dorsal interosseous muscle. The end result was assessed as just short of normal.

At least three factors must be presumed to be responsible for the delay between the reestablishment of anatomic continuity and the onset of voluntary contraction: (1) changes in the structure of the nerve fiber leading to functional maturation, (2) analogous change at the end organ leading to effective union with muscle fibers, and (3) (probably) a minimum number of mature fibers must be present before voluntary contraction appears. But, in the absence of histologic examination of the nerve fiber and the end organ during the crucial period of recovery, it cannot be determined in what proportion these factors are responsible.

Myelination and the restoration of fiber diameter are known to influence conduction, and there is ample evidence that these processes advance down the distal stump at a later date than does growth of

the axon tip.¹² According to Ramón y Cajal,⁷ "growth in diameter continues long after the appearance of the medullary sheath." Other factors of a more subtle character must also be taken into account. Thus, in the nerve lesions of the type defined by Seddon as neurapraxia, there may be complete interruption of conduction without wallerian degeneration or any significant morphologic change in the fiber (Denny-Brown and Brenner,¹³ Weiss and Davis,¹⁴ Seddon,¹⁵ Sunderland¹⁶).

The rate of regeneration, as calculated by Gutmann and associates,^{2a} varied according to the method used; this difference the authors attributed to the difference in the structure of the conducting fiber at different stages. The "pinch" method, which gave a faster rate, was shown by histologic examination to be applicable to axon tips. The other methods, however, depended on reflex activity, and the slower rates obtained were attributed to a presumed necessity for fully matured fibers. There is no convincing evidence, however, either that such reflex activity depends on a completely matured pathway or that it is not as efficiently served by an immature axon. In their experiments the growth of the axon tips was studied for shorter times and over shorter distances than was the rate of "advance of functional completion." Clinical observations indicate that the rate of regeneration is high at first and decreases later. In the animal experiments the rate was calculated for axon tips during brief periods at the beginning of growth, when the rate is most rapid. The higher rate for the axon tips is therefore not surprising; had the experiments been prolonged, it probably would have decreased and given a slower over-all rate.

It is generally accepted that Tinel's sign provides evidence of the presence of "young axis-cylinders in the process of regeneration," though there has been no histologic confirmation of this. Assuming this to be so, an advancing Tinel sign may be employed for determining the rate of advance of bare axons. Seddon, Medawar and Smith^{2b}

12. Howell, W. H., and Huber, G. C.: A Physiological, Histological and Clinical Study of the Degeneration and Regeneration in Peripheral Nerve Fibers After Severance of Their Connections with the Nerve Centers, *J. Physiol.* **13**: 335-406, 1892. Lewis, D., and Kirk, E. G.: Regeneration of Peripheral Nerves: An Experimental Study, *Tr. Am. S. A.* **34**:486-536, 1916. Sanders, F. K., and Young, J. Z.: The Degeneration and Reinnervation of Grafted Nerves, *J. Anat.* **76**:143-166 (Jan.) 1942. Weddell and others.¹¹ Ramón y Cajal.⁷

13. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, *Arch. Neurol. & Psychiat.* **51**:1-26 (Jan.) 1944.

14. Weiss, P., and Davis, H.: Pressure Block in Nerves Provided with Arterial Sleeves, *J. Neurophysiol.* **6**:269-286 (July) 1943.

15. Seddon, H. J.: Three Types of Nerve Injury, *Brain* **66**:237-288 (Dec.) 1943.

16. Sunderland, S.: Traumatic Injuries of Peripheral Nerves: I. Simple Compression Injuries of the Radial Nerve, *Brain* **68**:56-72 (March) 1945.

expressed the belief that "the wave front for Tinel's sign should . . . be well in front of that for motor and sensory fibers that have advanced to functional maturity." This, however, was not supported by their results, since they found that after suture axon tips advanced at an average rate of 1.71 mm. per day, while the rate of advance of functional maturity, based on the return of contraction of voluntary muscle after suture, was 1.6 ± 0.2 mm. per day. In a previous paper,^{1c} I presented data from which it was tentatively inferred that the rate for an advancing Tinel sign did not differ significantly from that provided by a study of voluntary motor function. At that time due weight was not assigned to two factors which the accumulated evidence has now shown to be all-important in affecting a comparison of the rates. These, as will be demonstrated in a subsequent section, are: (1) the length of nerve over which the rate is measured, and (2) the levels at which the measurements are taken.

A more detailed analysis of the data (table 5) on this basis has shown that the rate of advance of the bare axon is well in advance of the rate of functional maturation; this was more apparent in the cases in which both Tinel's sign and the return of voluntary contraction could be observed in the same subject (case 290, tables 3 and 5).

Conclusion.—From an analysis of all the information, it is evident that the regeneration of the axon and the maturation of the axonal pathway, on which the restoration of function depends, occur as two separate events in the process of repair. Maturation involves further morphologic changes of a complex character, such as myelination and the restoration of the fiber diameter, which proceed at a slower rate than does the advance of the bare axon.

FACTORS RESPONSIBLE FOR INDIVIDUAL VARIATIONS IN RATE OF REGENERATION AND FOR ITS PROGRESSIVE DECLINE THROUGHOUT THE PROCESS OF REPAIR

The rate of regeneration of nerve fibers is controlled by a number of factors which lead to individual variations, but it seems to be a general rule that the rate diminishes progressively in any one case. The capacity of the neuron to reform the injured fiber and the progress of the axon tip along the peripheral stump are the result of the combined action of two forces:

1. The activity of an especially organized growth cone, constituting the axon tips, which, as it descends, leads to the elongation of the axoplasm. Though localized at the extremity of the process, this activity requires for its effective control dynamic impulses from the cell body. This factor accounts for the multiple exploratory prolongations which sprout from each axon tip during regeneration and for the manner in which each seeks the path of least resistance distally, though this

also appears to be influenced mechanically by tissue lines of stress.¹⁷ When the axon tip finds a suitable pathway, it progresses at a rapid rate. The most suitable pathway is that provided by the neurilemmal tubes, and there is some evidence that axons seek Schwann cells in preference to all other tissues. This should not be surprising in view of the fact that a covering of these cells is essential for the proper functioning of all peripheral nerve fibers. The recent observations of Denny-Brown¹⁸ suggest that the cells which ensheath the newly formed axons are not mature Schwann cells but the neural fibroblasts which abound as the result of the proliferation of the connective tissue cells of the perineurium and endoneurium and which, by flattening themselves around the axis-cylinders, become Schwann cells.

2. Central changes in the cell which propel the axon tip distally. This factor has been recognized by a number of authors under different names—the law of continuous growth of His¹⁹ and Ramón y Cajal⁷; the *vis a tergo* of Held²⁰; the axonal turgescence of Dustin^{17c}; the histodynamic impulse of Heidenhain,²¹ and the turgor pressure of Young.²² More recently, Weiss and Taylor²³ have reported observations which suggest that “a growing fiber requires continuous contributions from its central cell body, the throttling of which entails a corresponding reduction of growth and myelinization.”

Connection with the cell body is a prerequisite on which the life of the fiber depends, and the transmission of the vital impulse appears to be associated with an appreciable intracellular pressure. That this pressure is appreciable is suggested by the outflow of axoplasm when the fiber is severed and by the herniation of the intrafunicular contents when the perineurium is breached. The endoneurium is very thin and, alone, would have difficulty in withstanding the lateral thrust of the intracellular factor. In order to compensate for this weakness, the

17. (a) Ranvier, L. A.: *Leçons sur l'histologie du système nerveux*, Paris, F. Savy, 1878, vol. 2. (b) Vanlair, cited by Ramón y Cajal.⁷ (c) Dustin, A. P.: *Le rôle des tropismes et de l'odogenèse dans la régénération du système nerveux*, *Arch. de biol.* **25**:269-388, 1910. (d) Weiss, P.: *In Vitro Experiments on Factors Determining Course of Out-Growing Nerve Fiber*, *J. Exper. Zool.* **68**:393-448 (Aug. 5) 1934.

18. Denny-Brown, D.: Importance of Neural Fibroblasts in the Regeneration of Nerve, *Arch. Neurol. & Psychiat.* **55**:171-215 (March) 1946.

19. His, W., cited by Ramón y Cajal.⁷

20. Held, H., cited by Ramón y Cajal.⁷

21. Heidenhain, M.: *Plasma und Zelle*, Jena, Gustav Fischer, 1911, vol. 2, p. 687.

22. Young, J. Z.: Contraction, Turgor and the Cytoskeleton of Nerve Fibers, *Nature*, London **153**:333-335 (March 18) 1944.

23. Weiss, P., and Taylor, A. C.: Impairment of Growth and Myelinization in Regenerating Nerve Fibers Subject to Constriction, *Proc. Soc. Exper. Biol. & Med.* **55**:77-80 (Jan.) 1944.

fibers are tightly bound into a compact funiculus which is ensheathed by perineurium, the strength of which is a feature of the mesodermal supporting framework of the nerve. Further evidence of a "translatory movement of axoplasm" under the influence of central forces is provided by the swelling which appears proximal to the constriction of a fiber.²³

Since the regeneration of axons is largely a manifestation of forces which proceed from the cell body, it is clear that the rate of growth will be proportionate to (1) the capacity of the cell to reform its fiber and (2) the tissues through which the axons must pass and which constitute the peripheral resistance which must be overcome by the intrinsic forces of growth.

FACTORS AFFECTING CAPACITY OF THE CELL TO REFORM THE INJURED FIBER AND RATE AT WHICH THIS IS EFFECTED

Age.—In general, the rate of growth is influenced by the age of the organism, being maximal in early life and slowly declining later. The results of Gutmann and associates²⁴ indicate that the rate of advance of axon tips down the nerve is of the same order in both young and old and that the rapid recoveries observed in young animals are more likely to be due "to great shortening of the delay in the suture scar, and probably acceleration of functional completion, combined, of course, with the fact that the distances to be covered are small." Whether or not the rate of regeneration of human nerves is more rapid in the young remains to be proved; no evidence on this point has been provided in the present series.

Chemical Agencies.—The vitality of the axon is influenced by deficiencies of vitamins and other essential factors in the body fluids and by the presence of toxins. No positive evidence is available, however, as to the extent to which regeneration of injured nerves could be affected by such factors, which did not operate in any of the present series of cases.

Temperature.—Deineka²⁴ expressed the belief that a rise in temperature increased the activity of regeneration. While the present material did not permit a study of these influences, the thermal variations between summer and winter appeared to have no effect.

Duration of the Period of Denervation.—The studies of Holmes and Young²⁵ have shown that the capacity of the central stump to throw out axon sprouts is not affected by the period of denervation. There is little information, however, relating to the rate of advance of

24. Deineka, D.: L'influence de la température ambiante sur la régénération des fibres nerveuses, *Folia neurobiol.* 2:13-24, 1908.

25. Holmes, W., and Young, J. Z.: Nerve Regeneration After Immediate and Delayed Suture, *J. Anat.* 77:63-96 (Oct.) 1942.

sprouts whose appearance has been delayed. Tables 2 and 3 contain data which demonstrate (1) that the capacity of the central stump for sprouting is retained for long periods and (2) that, after short and long periods of denervation, there may be little difference in the time taken to cover corresponding segments of the nerve (which is a measure of the rate).

It is possible that after very long delays the capacity of the cells to propel the axon distally may have waned, with a consequent reduction of the velocity of growth. Whether such a reduction, however, is to be assigned to an intrinsic factor, or solely to factors operating in the peripheral stump, remains obscure.

Level of Lesion and Length of Time for Which Nerve Has Been Regenerating.—Evidence has been obtained which suggests that the rate at which regenerating fibers advance through a given segment of a nerve is not influenced by the level at which the nerve is injured. In a series of cases, the interval between the first appearance of recovery in two muscles innervated by the injured nerve was compared with the level of the injury; an example for this purpose was provided by the intrinsic muscles of the hand, the time recorded being the interval between the appearance of recovery in the hypothenar group of muscles and its appearance in the first dorsal interosseous muscle (table 3). Whether the lesion of the ulnar nerve was high or low (considering the cases of axonotmesis and those of suture separately), this interval did not vary significantly. Thus, the level of the injury does not affect the rate in any given segment of the nerve. Furthermore, since in these cases regeneration had been proceeding for a longer period in the high lesions, these observations also indicate that the length of time for which the nerve has been growing is not a factor influencing the rate.

Distance of Growing Axon Tips from Parent Neurons.—It has been shown that there is a relationship between the progressive diminution of the rate of regeneration and the distance of the growing axon tips from their cell bodies. Thus, the initial rate is faster when the lesion is close to the parent neurons and slower when the lesion is more remote. In the former case, the rate slowly diminishes and, on reaching the more distal level, approximates the commencing rate of regeneration for a lesion in that segment. This diminution in rate could be attributed to the progressive decline, as the distance of the axon tips from the cell body increases, of the two factors on which its advance depends, namely, (a) the capacity of the cone of growth for active movement and (b) the intracellular pressure propelling it distally.

It follows from the last two considerations that, though the level of the injury does not affect the rate in any given segment of the nerve, it influences the initial velocity, which is greater with high than with low lesions. Furthermore, two factors, which greatly influence the

result, are constantly operating in any calculation of the rate: (a) the length of nerve over which the rate is calculated and (b) the levels at which the measurements are taken. These two factors must always be considered when one is comparing rates of regeneration.

FACTORS CONSTITUTING PERIPHERAL RESISTANCE WHICH
INTRINSIC GROWTH FORCES MUST OVERCOME

Factors Operating at Site of Injury.—Ramón y Cajal⁷ observed that advancing axons were retarded as they traversed scar tissue. It has recently been demonstrated that localized constriction of a nerve "deprives that part of a regenerating fiber lying beyond it of some factor essential for its further growth in width and myelination."²³ Whether or not the rate of longitudinal growth was also retarded was not determined, but there was sufficient evidence to suggest that functional maturation certainly would be delayed.

There is some evidence that growth along the peripheral stump is impeded by fibrosis of the nerve at the site of injury. Thus, the rate of regeneration following axonotmesis is greater than the rate following suture; with axonotmesis scarring at the site of injury is minimal, while with suture the scar at the site of union is more pronounced. Presumably, if the axon is forced distally under the influence of central changes, the scar tissue could, by acting as a sieve, introduce a constrictor effect on the growing fibers which would be continuously applied throughout the reconstitution of the axonal pathway and which would result in a reduction of the rate of advance of functional maturation.

In the absence of histologic examination of the injured segment of a nerve it is difficult to assess the severity of the lesion. The amount of extraneural injury is not a reliable guide, since minor lesions to the nerve are often associated with severe damage to tissue, and vice versa. The duration of the latent period, however, suggests a basis for comparison, the lesion being judged severe when the latent period is prolonged and mild when it is short. The important components of the latent period in this connection are (a) the initial delay and (b) the growth time; the remaining component (c), the terminal delay, depends on the duration of the other two, rising as they increase and falling as the period of denervation decreases (see later discussion).

The slower rate of advance of maturation down the distal segment following suture as compared with that following axonotmesis suggests that the severity of the lesion does affect the velocity, and there is some reason for attributing this slower rate to scar tissue at the site of union.

On the contrary, there is evidence that, within the axonotmesis and the suture group (each considered separately) the severity of the lesion may vary considerably without apparently influencing the rate.

Thus, in a number of cases of axonotmesis at approximately the same level of the ulnar nerve, though there was great disparity in the latent periods, the time taken to travel the distance between the same two muscles was approximately the same. Here, the great disparity in the latent periods could be due to variations in one of, or to a combination of, the following factors: (a) the initial delay, (b) the growth time and (c) the terminal delay.

An increase in the latent period means an increase in the terminal delay, which, in turn, signifies a proportionate increase in the time occupied by the initial delay and growth. In the cases cited, however, significant differences in the time of growth, and therefore in the rate, are unlikely, because the lesions were at about the same level, and approximately the same time was taken to travel the distance between the same two muscles, individual variations in the distances to muscles being too small to be significant. It is reasonable, therefore, to assume that the variations in the latent period involve corresponding variations in the initial delay and that these are indicative of the severity of the nerve lesion. As already pointed out, despite these variations in the initial delay, and therefore, presumably, in the severity of the lesion, the rates in the cases referred to remained substantially the same. Assuming, on the basis of the results following suture, that scar tissue is responsible for slowing the rate, it would appear that an increased initial delay after axonotmesis is not due solely to an increase in the elements obstructing the passage of the regenerating fibers; such an assumption is consistent with the appearance of the nerve at exploration and with the resultant restoration of function. The morphologic basis of the variations in the initial delay in cases of axonotmesis remains obscure, but it seems that, in some injuries at least, there are factors operating which do not affect the rate.

That variations in the initial delay do not invariably affect the rate following suture is suggested by the findings in the following case:

CASE 322.—O. A. R. sustained a gunshot wound of the upper third of the left arm on Oct. 21, 1944, which completely severed the ulnar and median nerves and the brachial artery. On Feb. 21, 1945, the median nerve was sutured under moderate tension, and the ulnar nerve, under such considerable tension that it was thought advisable to reexplore and resuture it on June 6, 1945, at which time the union was effected without tension. The nerves were sutured at about the same level. The advance of the axons was traced by following Tinel's sign distally. The sign was elicited 200 mm. below the union of the ulnar nerve one hundred and thirteen days after suture and 180 mm. below the union of the median nerve two hundred and eighteen days after suture. The difference in the distances covered could have been due to the faster growth of the ulnar axons. On the other hand, it could be attributed to the more accurate operative apposition of the stumps of the ulnar nerve, with improved conditions at the site of union, thereby resulting in a shorter initial delay; that this is the more likely explanation is supported by the observation that farther distally the calculated rates for the two nerves approximated (table 5).

Infection and Scarring: If a comparison is made of the progress of recovery in cases in which wound infection and scarring are significant, on the one hand, and the progress in cases in which these factors are absent or insignificant, on the other, it will be seen that they are inconstantly related to those factors which signify a slower rate (e. g., the time taken to travel the distance between the same two muscles). It seems that wound infection and scarring, in themselves, are not necessarily factors of importance in retarding the process of repair; their effect would appear to depend on the extent to which they add to the severity of the nerve lesion.

Conclusions: The rate of growth for corresponding sections of the nerve after suture is slower than that after axonotmesis. This seems to be due to factors operating at the site of union which appear to be associated with tissues obstructing and constricting the axons passing through them.

The duration of the initial delay following axonotmesis and suture (each considered separately), which is a guide to the severity and extent of the damage, may vary considerably without significantly affecting the ensuing rate of advance of maturation. It has been deduced that the morphologic changes which are responsible for variations in the initial delay in cases of peripheral nerve lesions are not the same as those responsible for the slower rate observed after suture as compared with that after axonotmesis. The morphologic basis of such variations remains obscure, but it seems that, in some injuries at least, the factors operating are such that the subsequent rate of advance of maturation along the distal segment, both for the initial stage and for the diminution that follows, is not significantly affected.

The progress of repair is adversely affected by wound infection and scarring only when, and so far as, these factors add to the severity of the nerve lesion.

Factors Operating in Peripheral Segment.—Holmes and Young²⁵ have shown that the total diameter of the peripheral stump shrinks during degeneration and that the neurilemmal tubes of which it is composed contract progressively if the stump remains uninervated. The reduction of the lumen of each tube not only increases the resistance to the downgrowth of the axon which enters the tube but also delays or prevents the restoration of its diameter and myelination, on which two factors maturation greatly depends.

After axonotmesis, significant shrinkage of the neurilemmal tubes would be prevented by the early entry of regenerating axons. It should be noted that a long latent period in these cases does not necessarily signify a long period of denervation of the peripheral stump, since this period has been measured in terms of returning function (i. e., maturation) and not in terms of the growth of the axon. Perhaps

the shrinkage of the neurilemmal tubes contributes to the progressive diminution of the rate of regeneration, in that the distal segments of the distal stump, being denervated for longer periods than the proximal segments, will be narrower and so offer more resistance. Whether such a factor is responsible for a diminishing rate of growth is by no means certain; it would seem that the early entry and descent of the axon would prevent the shrinkage occurring to a degree to which it could influence the rate in the manner specified. Conditions similar to those after axonotmesis might be said to obtain after early suture. The interval between the times of functional reinnervation of the same two muscles after early suture is, however, greater than that after axonotmesis (axonotmesis and suture, ulnar group, table 3). Furthermore, in cases of late suture the conditions are different in that the neurilemmal tubes have had ample time to shrink before the entry of axons. In these circumstances, it is to be expected that the rate would be slower after late than after early suture, so that the interval between the times of functional reinnervation of the same two muscles would be much greater in cases of late suture. When cases of early and cases of late suture are compared, however, there is often no significant difference in this interval; and when there is, the longer interval is as often associated with the early as with the late suture.

There is good reason, therefore, for believing that the slower rate after suture is due not to an increase in the resistance presented by the peripheral stump but to factors related to the site of suture and probably to the scar tissue, which exerts a constrictor effect. These observations also throw doubt on the role of neurilemmal shrinkage as an agent in adversely affecting the recovery after suture.

• GENERAL CONCLUSIONS

The velocity of growth is the resultant of (1) central forces provided by the cell body and (2) the peripheral resistance against which the central forces of growth act. An important peripheral factor leading to a reduction in the velocity is constriction at the site of injury due, for example, to scar tissue. This constriction may be internal or external; the relief of the latter may account for some of the rapid recoveries following neurolysis.

The progressively diminishing velocity of growth which occurs throughout the process of repair could be due to a reduction in the pressure operating from within the cell body or to a peripheral resistance which increases progressively along the peripheral stump. These observations suggest that the diminishing rate is principally the result of waning central forces of growth, which are reduced as the axon lengthens, and that the decline is not significantly contributed to by any peripheral factor in the distal stump below the site of the lesion.

Furthermore, it has been concluded that it is not the length of time for which the nerve has been regenerating which is the factor controlling the rate, but the distance of the growing axon tips from their parent cells.

Though the level of the lesion does not appear to affect the rate over any given section of the nerve, it is closely related to the initial velocity of regeneration. Thus, the rate in the initial stages of recovery is faster with high lesions, since these are close to the parent neurons, whereas when the lesion is at a lower level the initial rate is slower because the influence of the central forces of growth is weaker.

Two important factors influence a calculation of the rate: (a) the length of nerve over which the rate has been measured and (b) the level at which the measurements are taken. Both factors must always be taken into consideration when attempting a comparison of the rates of regeneration in any 2 instances.

THE LATENT PERIOD

The latent period, or interval between the date of injury and the onset of clinical recovery, comprises (a) the initial delay, (b) the period of growth and maturation and (c) the terminal delay. Differences in the latent period could be due to variations in any of these components.

Time Occupied by Growth and Maturation of Axon.—The time occupied by the growth and maturation of the regenerating fibers can be calculated from a knowledge of (a) the level of the injury with reference to a bony point, (b) the distance from this point to the structure to be innervated and (c) the rate of regeneration. In calculating the growth time in any individual specimen, there are two unpredictable sources of error: (1) individual variations in the distance to the muscles and (2) individual variations in the rate and variations imposed by the severity of the injury. In the present investigation average distances and average rates have been employed; for this reason, the calculated growth time from which the duration of the combined initial and terminal delay was derived must be regarded as approximate. Furthermore, despite the evidence that the rate following suture is slower than the rate following axonotmesis, no distinction has been drawn between the two in calculating the growth time owing to the small number of cases of suture, which renders useless any attempt to obtain a precise average rate for the different segments of each peripheral nerve. The following rates have been used in all calculations: 3 mm. per day for the upper part of the arm and the thigh; 2 and 1.5 mm. per day for the regions about the elbow and knee, respectively; 1 mm. per day for the leg and forearm, and 0.5 mm. per day for the hand and for the lower part of the leg and the foot.

When the time occupied by growth and maturation is subtracted from the latent period, the result is the combined initial and terminal delay. It is difficult to assess the relative contributions of each component in the combined delay, since there is no known clinical method of calculating the two independently, though electromyography may be developed to prove valuable for this purpose.

Initial Delay.—Immature axons cross the injured zone before the process of maturation commences. According to Ramón y Cajal's⁷ experimental observations, "one sees with certainty the axons in the peripheral stump . . . only from the 12th to the 15th day" after suture, while Perroncito²⁶ and Lewis²⁷ reported their entry after the sixth and by the fourteenth day. Gutmann and associates,^{2a} in calculating the initial delay (which they termed latent period), employed methods of extrapolation the weaknesses of which have been pointed out. They gave values of 7.27 days following plasma suture and 5.23 and 2.35 days in old and very young rabbits, respectively, after crushing.

If Tinel's sign indicates the presence of regenerating axon tips, it should provide an ideal guide to the entry of immature axons into the distal segment. Seddon and associates^{2b} obtained a negative initial delay by using this method; it appears, however, that they were misled by their assumption that the rate of growth was constant, and therefore representable on their graphs by a straight line. In only 1 case of the series which I studied (9 cases of suture and 3 in which the nerve was in continuity) was the sign observed soon after its appearance; it was elicited 15 mm. below the suture thirty-three days after union. If the rate of growth was 3 mm. per day, the initial delay would have been twenty-eight days. In the remaining cases the axons had advanced over considerable distances before the descent of Tinel's sign was recorded metrically. The calculation of the initial delay in these cases of regenerating axons involves the estimation of the time occupied by growth, for which it is necessary to take into consideration any significant decline in the rate. This is difficult, since the rate could not be calculated over the section of the nerve extending from the lesion to the first measured point where Tinel's sign was elicited (for which a knowledge of the initial delay would be necessary). To overcome this, a constant rate of 3 mm. per day was used for obtaining values for the initial delay, which must, therefore, be regarded as approximate only. The values were: (1) lesion in continuity: six, two hundred and twenty-five, and two hundred and eighty-seven days; (2) after suture: three, fifteen, twenty-one, thirty-six, forty, forty-two, forty-six, and

26. Perroncito, A.: Die Regeneration der Nerven, Beitr. z. path. Anat. u. z. allg. Path. **42**:355-466, 1907.

27. Lewis, D.: Principles of Peripheral Nerve Surgery, J. A. M. A. **75**:73-77 (July 10) 1920.

one hundred and fifty-eight days. Using Tinel's sign to detect the first appearance of axons in the peripheral stump, Dustin^{8b} found that the initial delay after a good suture varied from thirty to sixty days.

There is, therefore, reliable evidence that after the suture of human nerves the entry of axon tips into the peripheral stump may be delayed for periods far exceeding those observed experimentally.

It is more difficult to assess the time required for the maturation of the axons in the central stump and injured zone. Reference has been made to the experimental efforts of Gutmann and associates^{2a} to calculate the initial delay by extrapolation. From a study of returning sensory function following a crush injury, they obtained an initial delay of 9.76 days in one set of experiments and 19.0 days in another. A study of returning reflex motor activity gave initial delays as follows:

After crushing: 20.77 and 21.6 days in adults and 10.2 days in the very young

After suture: 32.35 and 36.5 days in adults and 16.2 days in the very young

Attention has already been directed to the unsatisfactory features of this method of calculation. Furthermore, there is no evidence that the recovery of reflex activity requires a degree of maturation comparable with that demanded for the recovery of function as studied in human material.

Seddon and associates^{2b} also used extrapolation in their estimation of this period in clinical material. Excluding the cases in which a negative reading was obtained, extrapolation gave the following values for the radial nerve:

After axonotmesis: 25, 29, 69, 71, 103, 185 and 218 days, with average of approximately 14 weeks

After suture: 68, 80, 132, 135, 151 and 155 days, with average of approximately 17 weeks

In a later section in their paper, these authors gave "six or eight weeks for an unduly long latent period" in cases of axonotmesis of the radial nerve. This inconsistency was not explained.

Though the initial delay for matured fibers defies precise measurement, there is evidence, other than that provided by extrapolation, that it varies from one person to another. Thus, when the same nerve in 2 cases (for example cases 176 and 235, both cases of axonotmesis of the ulnar nerve with a concomitant bone injury due to a gunshot wound) has been injured at different levels, the reappearance of contraction in the same muscle (for example, the hypothenar group) may occur after about the same interval, differences appearing in the calculated combined initial and terminal delays in these cases. The following factors could be contributory:

1. Individual differences in the rate of growth and in the distance to the muscle. Despite the possibility of such variations, it is most unlikely that they would be of sufficient magnitude to account for the observed differences in the delay.

2. Variations in the terminal delay. Since the same muscle is involved (admittedly, with possibly differing intramuscular factors in different persons) and the period of denervation is substantially the same, it is reasonable to assume that any difference in the terminal delay would be so small as to be unimportant.

3. Variations in the initial delay. This would appear to be the most probable explanation of the difference in the duration of the combined delay. In a previous section relating to the effect of the severity of the lesion on the ensuing rate of regeneration, it was also deduced that the initial delay is subject to variation.

Conclusions: Analysis of the available evidence indicates that the initial delay for both axon tips and the matured fiber may vary from a few days to several months. Governing factors are the extent and density of the obstructing tissues in the injured segment of nerve, the length of the injured segment and the amount of retrograde degeneration. These morphologic features are, in general, related to the causative injury. Excluding the exceptions, the evidence suggests that these changes are minimal in minor injuries and maximal in stretch injuries and in injuries due to severe gunshot wounds with a concomitant bone injury, prolonged infection and considerable scarring. That the factors which are responsible for the duration of the initial delay are often more complicated than the morphologic changes referred to is suggested by the cases in which a prolonged initial delay is not associated with any alteration in the rate, with any permanent defect of function or with any change in the nerve which could be detected at operation by inspection and palpation.

Terminal Delay.—The terminal delay comprises the time required for (1) regeneration in the muscle from the surface to the end organ and (2) recovery of capacity for effective contraction of reinnervated muscle fibers.

Gutmann and Young²⁸ demonstrated in the rabbit that after a crush injury close to the muscle, "fibers arrive back near the end-plates about 12 days after the operation, whereas electrical stimulation of the nerve produced contraction first on the 18th day and reflex functioning appeared on the 23rd day." They stated that the corresponding times after suture were greater and that these steadily increased with increasing periods of denervation.

28. Gutmann, E., and Young, J. Z.: The Re-Innervation of Muscle After Various Periods of Atrophy, *J. Anat.* 78:15-43 (Jan.) 1944.

No precise data relating to these events are available in man. Though motor fibers run complicated, and often long, courses within the muscle before reaching their final destination, the distance to be covered before functional recovery follows is not known. The rate at which functional regeneration proceeds within the muscle is also not known; it probably does not differ greatly from that just external to the muscle. Thus, in muscle innervated in the vicinity of the elbow and knee rates of approximately 2 and 1.5 mm. per day, respectively, may be expected; in the midforearm and leg, a rate of 1 mm. per day, and in the hand and foot, a rate of 0.5 mm. per day. In arriving at these estimates, it should be noted that the rate falls to a minimum as the length of the fiber increases and not necessarily as the terminal part of the fiber is being reconstituted; thus, the terminal portion of a very long fiber would be reconstituted at a very slow rate, while the corresponding portion of a short fiber would be laid down at a more rapid rate.

Another factor influencing the terminal delay in human material is the latent period, or duration of the period of denervation. In this connection, a study of the combined initial and terminal delay following axonotmesis for each of two muscles innervated at different levels along the same nerve has proved instructive. Since the initial delay in such cases is the same for each muscle, any significant difference in the combined delay could be attributed to an increase in the terminal delay occurring in the more distal muscle. Thus, in case 31 (injury of the ulnar nerve) the two muscles selected were the flexor carpi ulnaris and the hypothenar group. For each muscle, the distance from the lesion to the muscle, the rate employed in calculating the growth time, the period of denervation, the growth time and the calculated combined delay were tabulated.

Flexor carpi ulnaris: 133 mm.	2 mm.	27 wk.	10 wk.	17 wk.
Hypothenar group: 412 mm.	2 mm. for the first, 133 mm. and 1.0 mm. thereafter	80 wk.	50 wk.	30 wk.

Since the initial delay is the same, the greater combined delay in the case of the muscles of the hypothenar group could be attributed to the following factors:

1. An error in the growth time, owing to a greater decline in the rate of advance than that allowed for. The rate for the first 133 mm. would be the same as that for the fibers destined for both muscles, namely, 2 mm. per day (see criteria for selection of clinical material and its use in calculating rates of regeneration); even if the rate distal to this level were reduced to a figure just above that obtaining for the section of the nerve in the hand, the disparity in the combined delay would still be considerable.

2. Individual variations in the distances to the two muscles. These are too small to account for the magnitude of the difference in the combined initial and terminal delays.

3. An increase in the terminal delay. This is the most probable explanation, though the length of the delay will depend on the value assigned to (*a*) the growth rate and (*b*) the distances to the muscles.

Such an analysis of the data contained in tables 2, 3, 4 and 6 indicates that in human material the terminal delay rises with the period of denervation (latent period).

Finally, reference has been made in an earlier section to the electromyographic¹¹ studies, which indicate the entry of fibers into muscles prior to their recovery of voluntary contraction and, also, to the recovery of the excitability of the motor unit to direct stimulation of the nerve before the reappearance of voluntary contraction. To what extent the delay between the two phases of recovery is attributable to an intramuscular factor is not revealed by such studies.

These generalizations, while indicating the significance of the terminal delay as a contributing factor to the combined delay, do not permit a metrical expression of its value. The delay will be influenced by such factors as (*a*) the intramuscular distance to be traveled by the regenerating fibers and the rate at which they advance within the muscle; (*b*) the period of denervation [this depends on (1) the level of the injury, (2) the rate of regeneration of the axons and (3) the initial delay], and (*c*) the degree and pattern of reinnervation.

COMBINED INITIAL AND TERMINAL DELAY

For reasons emerging from the foregoing discussion, it has been considered preferable not to attempt any separation of the initial and terminal delays when analyzing the latent period, but to regard the two as comprising a combined period of delay in the process of repair. The same policy was adopted in a previous reference to this interval following lesions of the radial nerve, but in that study the term "initial delay" was employed to cover both the initial and the terminal delay.^{1a} It is now felt, however, that the use of this term to cover both components is confusing and that it would be preferable, therefore, to introduce the term "combined initial and terminal delay." In calculating the values for this period, which are given in table 6, cases were selected in which the lesions were relatively close to the first muscle innervated below the lesion. This was done for the following reasons.

(*a*) To minimize errors in the growth time which would be introduced over very long distances by an individual variation in the rate. Thus, over a distance of 300 mm. a rate of 1.5 mm. per day, as opposed to one of 1.0 mm. per day, would mean a difference of one hundred days in the growth time: over a distance of 90 mm. the difference would be thirty days.

TABLE 6.—*Data Employed in Estimating Relative Contributions to Latent Period of Growth Time and of Initial and Terminal Delays.*

Causative Injury; Nature of Nerve Lesion; Case No.	Level of Lesion, Mm.*	First Muscle to Recover †	Distance from Lesion to First Muscle to Recover, Mm.	Rate, per Day, Mm.	Latent Period	Combined Initial and Terminal Delay
Radial nerve						
(a) Axonotmesis						
Simple fracture of the humerus						
Case 77.....	100 above L. H. E.	BR.	82	2.0	16	10
161.....	100 above L. H. E.	BR.	82	2.0	13	7
317.....	100 above L. H. E.	BR.	82	2.0	16	10
Gunshot wound						
Case 185.....	120 above L. H. E.	BR.	102	2.0	14	7
203.....	90 above L. H. E.	BR.	72	2.0	20	15
255.....	20 above L. H. E.	BR.	2	2.0	8	8—
264.....	10 above L. H. E.	E. C. R. L.	15	2.0	14	13
Gunshot wound + fracture of humerus						
Case 100.....	75 above L. H. E.	E. C. R. L.	80	2.0	23	17
106.....	50 above L. H. E.	BR.	32	2.0	17	15
118.....	90 above L. H. E.	BR.	72	2.0	16	11
231.....	125 above L. H. E.	BR.	107	2.0	40	32
258.....	50 above L. H. E.	BR.	32	2.0	18	16
(b) Suture						
Laceration						
Case 180.....	40 above L. H. E.	E. C. R. L.	45	2.0	20	17
282.....	125 above L. H. E.	BR.	107	2.0	22	14
Gunshot wound						
Case 40.....	50 above L. H. E.	E. C. R. L.	55	2.0	20	16
Ulnar nerve						
(a) Axonotmesis						
Laceration						
Case 103.....	50 above R. S. L.	H.	82	1.0	20	8
323.....	20 below R. S. L.	H.	12	1.0	8	6
Gunshot wound						
Case 31.....	100 above M. H. E.	F. C. U.	133	2.0	27	17
237.....	80 above R. S. L.	H.	112	1.0	34	18
Gunshot wound + bone injury						
Case 235.....	10 above R. S. L.	H.	42	1.0	29	23
(b) Suture						
Laceration						
Case 139.....	10 above R. S. L.	H.	42	1.0	28	22
158.....	25 above M. H. E.	F. C. U.	58	2.0	18	14
290.....	At M. H. E.	F. C. U.	33	2.0	17	15
325.....	80 above R. S. L.	H.	112	1.0	40	24
Gunshot wound						
Case 38.....	80 above R. S. L.	H.	112	1.0	17	1
183.....	70 above M. H. E.	F. C. U.	103	2.0	28	21
207.....	60 above M. H. E.	F. C. U.	93	2.0	14	7
Gunshot wound + bone injury						
Case 100.....	60 above M. H. E.	F. C. U.	93	2.0	30	23
Sciatic nerve						
(a) Axonotmesis						
Compression						
Case 188.....	Neck of fibula	P. L.	19	1.5	21	19
		T. A.	28	1.5	21	18
245 (right leg)	Neck of fibula	P. L.	19	1.5	20	18
245 (left leg)	Neck of fibula	P. L.	19	1.5	18	16
		T. A.	28	1.5	18	15
Simple fracture of femur						
Case 326.....	100 above M. F. E.	G.	181	1.5	29	17
Gunshot wound						
Case 82.....	Head of fibula	P. L.	19	1.5	18	16
		T. A.	28	1.5	18	15
95.....	50 above M. F. E.	G.	81	1.5	15	7
		P. L.	144	1.5	19	5
109.....	70 above M. F. E.	G.	101	2.0	13	6
190.....	At M. F. E.	G.	31	1.5	22	19
254.....	Head of fibula	P. L.	19	1.5	7	5
		T. A.	28	1.5	7	4
Gunshot wound + bone injury						
Case 260.....	50 above M. F. E.	G.	81	1.5	12	4

* L. H. E. indicates the lateral epicondyle of the humerus; R. S. L. and M. H. E., the level of the styloid process of the radius and the medial epicondyle of the humerus, respectively, and M. F. E. the medial epicondyle of the femur.

† BR. denotes brachioradialis; E. C. R. L., extensor carpi radialis longus; H., hypotenar muscles; F. C. U., flexor carpi ulnaris; P. L., peroneus longus; T. A., tibialis anterior; G., gastrocnemius.

(b) To minimize errors due to the declining rate, which would increase with the length of the nerve.

(c) To shorten the period of denervation, which would reduce the duration of the terminal delay.

The combined delay varied from one to thirty-two weeks, with a mean of thirteen weeks following axonotmesis and sixteen weeks following suture.

Influence of Infection and Scarring.—It is difficult to assess the effect of wound infection and scarring on the duration of the latent period, since there were cases in which despite their absence the latent period was prolonged, whereas there were other cases in which severe infection and scarring were associated with a very short latent period. The principal factor affecting the duration of the latent period is the severity of the nerve lesion. The effect of infection and scarring will, therefore, depend on the extent to which they add to the severity of the nerve lesion. For this reason their influence is variable. It may be concluded that while wound infection and scarring may increase the hazards of repair and the duration of the latent period, there is reliable evidence that they may be severe without retarding the progress of recovery.

Conclusions.—The combined initial and terminal delay varied from one to thirty-two weeks, with a mean of thirteen weeks, following axonotmesis and sixteen weeks after suture. It rose as the distance of the lesion from the muscle increased; this was due to an increase in the terminal delay consequent on an increase in the period of denervation.

The combined delay was of longer duration in the cases of severer lesions. This is attributed to the following factors:

1. An increased initial delay, which, in turn, may be due to an increase in the amount, extent and density of obstructing tissues in the injured segment or to factors which do not result in the same gross pathologic change.
2. An increase in the terminal delay occasioned by an increase in the period of denervation. The increase in the period of denervation is due to the increased initial delay and to the slower rate of growth of axons when this is associated with it.

SUMMARY

A. Methods previously employed to calculate the rate of regeneration are reviewed in detail, with especial reference to those used to study this process in human peripheral nerve injuries.

B. From a study of the rate of regeneration in a series of human peripheral nerve injuries, the following conclusions are made:

1. There are two separate events in the process of repair: (*a*) regeneration of the axon, and (*b*) functional maturation of the axonal pathway, which involves further morphologic changes of a complex character, such as myelination and the restoration of fiber diameter. The second process proceeds at a slower rate than does the advance of the axon.

2. The velocity of regeneration for both processes diminishes progressively over the whole period of recovery.

3. There is a relationship between the progressive diminution of the rate of regeneration and the distance of the growing axon tips from their cell bodies. Thus, the initial rate is faster when the lesion is close to the parent neurons and slower when the lesion is more remote. In the former case, the rate slowly diminishes and, on reaching the more distal level, approximates the beginning rate of regeneration for a lesion in that segment.

4. After axonotmesis, the rate of advance of functional maturation over the proximal portion of the nerve (arm and thigh) is in the vicinity of 3 mm. per day and slowly diminishes to approximately 0.5 mm. per day over the distal portion (hand and foot). The rate following suture is slower for all sections of the nerve—it was, however, not possible to ascertain precisely to what extent this was so.

5. After suture, the axon tips advance down the forearm and leg at a rate, in the vicinity of the elbow and knee, of approximately 3 and 2 mm. per day, respectively, but this rate gradually slows until at the wrist and ankle it is commensurate with that observed for functional completion.

C. The factors responsible for individual variations in the rate and for its progressive decline throughout the process of repair are discussed in detail.

1. The velocity of regeneration is the resultant of (*a*) central forces provided by the cell body and (*b*) the peripheral resistance against which the central growth forces act.

2. The observations suggest that the diminishing rate is principally the result of waning central forces of growth, which are reduced as the axon lengthens, and that the decline is not significantly contributed to by any peripheral factor in the distal stump below the site of the lesion. Furthermore, it is not the length of time for which the nerve has been growing which is the factor controlling the rate but the distance of the growing axon tips from the parent cells.

3. An important peripheral factor leading to a reduction in the velocity is constriction at the site of injury, due, for example, to scar tissue, which may be situated within or around the nerve.

4. The level of the lesion does not appear to affect the rate over any given section of the nerve but is closely related to the initial velocity of regeneration. Thus, the rate in the initial stages of recovery is faster with high lesions, since these are close to the parent neurons, whereas when the lesion is at a lower level the initial rate is slower because the influence of the central forces of growth is weaker.

5. Two factors must always be taken into consideration when attempting a comparison of the rate of regeneration in any 2 instances: (a) the length of nerve over which the rate is calculated, and (b) the levels at which the measurements are taken.

D. The latent period, or interval between the date of injury and the onset of clinical recovery, is analyzed. It comprises (a) the initial delay, (b) the time occupied by the growth and maturation of the regenerating axons and (c) the terminal delay. All three components are defined and discussed.

1. Information required for the calculation, in any case, of the time occupied by the growth and maturation of the regenerating axon is provided.

2. For reasons fully set out, it is considered preferable not to attempt any separation of the initial and the terminal delay when analyzing the latent period, but to regard the two as comprising a combined period of delay in the process of repair.

(a) The combined delay varied from one to thirty-two weeks, with a mean of thirteen weeks after axonotmesis and of sixteen weeks after suture.

(b) The combined delay rose as the distance of the lesion from the muscle increased; this was due to an increase in the period of denervation.

(c) The combined delay was of longer duration with the severer lesions. This is attributed to two factors: (1) an increased initial delay, which, in turn, is probably due to an increase in the amount, extent and density of obstructing tissues in the injured segment. These morphologic features are in general related to the causative injury. Excluding the exceptions, the evidence suggests that these morphologic changes are minimal with minor injuries and maximal with stretch injuries and injuries due to severe gunshot wounds with concomitant bone injury, prolonged infection and considerable scarring. (2) An increase in the terminal delay occasioned by the increase in the period of denervation, which is due to the increased initial delay and to the slower rate of growth of axons when this is associated with it.

E. It is concluded that repair is adversely affected by wound infection and scarring only when, and so far as, these factors add to the severity of the nerve lesion.

A RATIONAL SUBDIVISION OF THE CEREBRAL CORTEX

PROF. I. N. FILIMONOFF

MOSCOW, UNITED SOVIET SOCIALIST REPUBLICS

THE STUDY of regional peculiarities of the structure of the cerebral cortex as revealed by certain features and the division of the cortex into structural units on the basis of these features constitute the main problem of the architectonics of the cerebral cortex. These features are of varying value. Some of them are of major importance and should form the basis for division of the cerebral cortex into main territories. Others are of more specific significance and serve to subdivide the main territories into regions, subregions, areas and subareas, according to a certain hierarchial order and depending on their relative importance. Finally, there is an enormous number of less important features, allowing subdivision of the cortex literally *ad infinitum*. As a matter of fact, no part of the cortex, however small it may be, exhibits absolute similarity to the neighboring part.

It would be possible to consider these structural modifications as special areas and subareas—all depends on one's understanding of the concept "area," which so far has no generally recognized definition. However, as I have already emphasized in one of my previous papers:

Von wesentlicher Bedeutung ist aber der Umstand, dass bei einer solchen allzu weitgehenden Differenzierung das Prinzip der Felderung selbst seinen Wert zu verlieren beginnt. Darum müssen hier gewisse Grenzen gesetzt werden, und die Arbeit muss nicht nur in der Richtung der Differenzierung, sondern auch in der Richtung der Integrierung vor sich gehen, d. h. der Vereinigung der kleiner Formationen, die sich voneinander nur durch unwesentliche Merkmale unterscheiden, in Formationen höherer Ordnung, deren Absonderung als Grund eine genügende Anzahl wesentlicher Merkmale wird (page 23).¹

"It is of essential significance that with too far reaching a differentiation the principle of division of the cerebral cortex into areas may lose its value. Certain limits are required, and work must be carried out in the direction not only of differentiation but also of integration, i.e., the unification of small formations, which are to be distinguished from one another only by unessential characteristics, into formations of a higher order, the separation of which may be justified by a sufficient number of essential characteristics."

But how can one judge whether these features are essential or not? Of course, their character as revealed by the architectonics of the adult brain is of great value in this respect, but it is the dynamics of the

1. Filimonoff, I. N.: Ueber die Variabilität der Grosshirnrindenstruktur: Regio occipitalis beim erwachsenen Menschen, J. f. Psychol. u. Neurol. 44:1-96 (Jan.) 1932.

development of architectonic formations which is of major significance. It is quite obvious that the earlier certain features appear in the process of development, the greater should be their importance for the division of the cortex into its main regions. It is significant in this respect that division of the cortex into two chief regions—the homogenetic and the heterogenetic cortex—a classification which represents the main principle of modern cytoarchitectonics, was founded by Brodmann on ontogenetic data. The well known classification of cortical structures by Rose is also based on the ontogenetic principle.

The classification which my colleagues and I have formulated² is likewise founded on the principle of ontogenetic development. Like the Rose classification, it is based on the study not only of late stages of ontogenesis, as in Brodmann's scheme, but also of early ones and takes into consideration both the development of the cortical plate and that of the entire wall of the end brain. Like the Rose classification, it leads to division of the cerebral cortex not into two, as in Brodmann's scheme, but into three, main territories. However, our classification is based on quite another concept than that of Rose, which, in our opinion, is particularly erroneous with respect to his "schizocortex." Rose considers this portion of the cortex in contrast to his "holocortex" and presented it in his scheme as a unit, including such actually heterogenous structures as the isocortex and Ammon's cortex. Our investigations would show that the relations are just the reverse: The schizocortex ("periarchicortex" in our terminology) occupies a place intermediate between Ammon's cortex (archicortex) and the isocortex, since Ammon's plate can by no means be considered as a homologue of the isocortical plate. Our understanding of the semicortex (cortex semiseparatus, not cortex semiparietinus in the sense of Rose) is also entirely different. The cortex bigenitus occupies an intermediate place between the isocortex and the allocortex both in our classification (perisemical zone) and in the Rose system (between the cortex totoparietinus and the cortex semiparietinus). However, we understand this intermediate position in a quite different sense, since our concept of the genetic character of the claustrum is quite a different one.

Hence, important peculiarities of structure are concerned in the difference between the two classifications, and, of course, many specific points of distinction as well, especially with respect to stratification of the entorhinal and, in part, of the presubicular region.

The main territories of the cerebral cortex are designated in our scheme as cortex completus or isocortex (after O. Vogt); cortex incompletus, or allocortex (after O. Vogt), but with considerable limitations (allocortex *sensu strictiori*), and cortex intermedius, or periallocortex.

2. Sarkisov, S. A., and Filimonoff, I. N.: Les travaux de l'Institut du cerveau, Moscow, Izdanie Gosudarstvennogo Instituta Mozga, 1938, vols. III-IV.

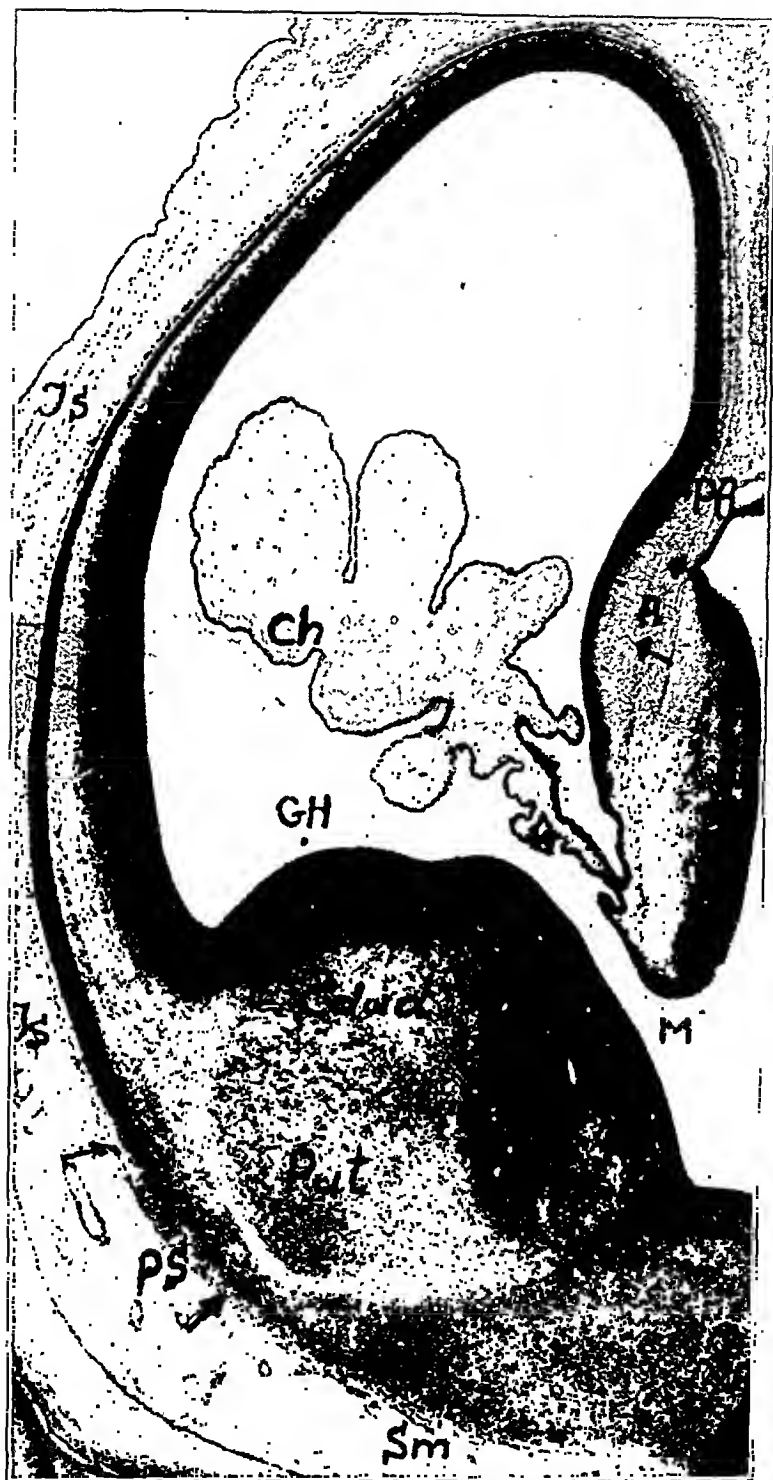


Fig. 1.—Stage, 35 mm. *A* is archicortex; *Caud*, caudate nucleus; *Ch*, choroid plexus; *Gh*, Hügel's ganglion; *Is*, isocortex; *M*, foramen of Monro; *PA*, peri-archicortex; *PS*, perisemicortex; *Put*, putamen, and *Sm*, semicortex.

The cortex completus, or isocortex, includes the whole territory within which the end brain wall is characterized, even in relatively early stages of development (27 mm. stage in our material), by the presence of all the fundamental layers of His, including the clearly differentiated cortical plate (fig. 1). On the contrary, the cortex incompletus, or allocortex *sensu strictiori*, shows incompleteness of the structure of the wall in the early stages, this incompleteness being maintained to a certain extent in subsequent stages of development, including the definitive stage. The third main territory—the cortex intermedius, or periallocortex, separates everywhere the cortex completus from the cortex incompletus and is characterized by a special type of transitional structure.

The cortex incompletus, or allocortex *sensu strictiori*, includes, first, the semicortex, or semicortical zone, to which belong the tuberculum of lactarium (*T*), the diagonal region (*D*), the septum pellucidum (*Spt*), the periamygdalar region (*Pm*) and the prepiriform region (*Pp*), but the latter only partly, since, as a matter of fact, it presents a transition from the semicortex *sensu proprio* to a cortex of higher type, namely, the cortex intermedius (perisemicortex; see later section). The second main territory of the allocortex is represented by the archicortex, or the archicortical, or Ammon's zone, which includes the subiculum (*Sub*), the cornu ammonis (*Ca*), the fascia dentata (*FD*) and the tenia tecta (indusium corporis callosi).

The incompleteness of the semicortical zone is manifested by non-separation (early stages of development), or by incomplete separation, of the cortical plate from the periventricular cell masses (cortex semi-separatus). The semicortical zone is genetically connected with the condensed external sublayer of the stratum intermedium (*Z*), termed by us *Z*¹, and not with the cortical plate of the isocortex. In early stages of development (27 to 35 mm., fig. 1) it is clearly seen that the dense sublayer *Z*¹, distinctly differing from stratum *Z* proprium in its scarcity of cells and disappearing into the latter at the level of the isocortex (*Is*), comes into immediate contact with the stratum marginale (*Randschleier* of His) at the level of the semicortex (*Sm*). Thus, the semicortex generally fails to exhibit a true cortical plate homologous with the cortical plate of the isocortex.

Incompleteness of the archicortex, or Ammon's zone, is also manifested in early stages of development and is subsequently maintained, though in a modified form. In early stages of development (27 to 35 mm.) the entire brain wall within the archicortical zone (fig. 1, *A*) exhibits extreme scarcity of cellular elements; the matrix is narrow, and the complete absence of a cortical plate is an outstanding feature. At the 55 mm. stage the cortical plate appears in the archicortex also, but it differs strongly from the isocortical plate in its rarefied character and in its relatively slight separation from the subjacent stratum inter-

medium. Hence the cortical plate of the archicortex is characterized, first, by a scarcity of cellular elements and, second, by its being formed, in contrast to the isocortex, by the secondary migratory wave of neuroblasts only, the latter feature being of no less importance. With respect to time of formation, it corresponds only to the deeper layer of the *cortex intermedius* (see later section). The fact that Ammon's plate corresponds not to the entire cortical plate of the *cortex intermedius* but only to its deeper layer is still more apparent during further development in the superlamination on Ammon's plate of the isocortical plate within the *cortex intermedius* (see later section; compare with figures 2 and 3).

The *cortex completus* and the *cortex incompletus* differ strongly during the process of development as well as in the adult stage, as has already been mentioned; they present no immediate contiguity and are separated from each other by intermediate structures, which can be referred neither to the *cortex completus* nor, even less, to the *cortex incompletus*, and which for this reason we regard as the third main territory, the *cortex intermedius*, or *periallocortex*. The *cortex intermedius*, separating thus the *semicortical* and *archicortical* zones (forming together the *cortex incompletus*) from the *cortex completus*, is divided, like the *cortex incompletus*, into two zones—the *perisemicortical* and the *periarchicortical* zone.

The whole cerebral cortex is thus divided into three main territories, or into five main zones: the *cortex completus*, or *isocortex*; the *cortex incompletus*, or *allocortex sensu strictiori*, including the *semicortical* and the *archicortical* zone, and the *cortex intermedius*, or *periallocortex*, including the *perisemicortical* and the *periarchicortical* zone.

The *perisemicortical* zone includes the intermediate insular formations and partly also the *prepiriform* region, which can thus be referred to the *semicortex* in a rather conventional sense.

The *periarchicortical* zone includes the *presubicular* and the *entorhinal* region.

The *presubicular* region (*Psb*) bears a strong transitional character even in very early stages of embryonic development (27 to 35 mm.), when it cannot yet be separated from the *entorhinal* region. In this still undifferentiated stage the cortical plate is already outlined, though weakly, into regions; the *periarchicortical* zone, in contradistinction to the *archicortex*, presents a larger number of cells (fig. 1, *PA*).

At the 55 mm. stage the *presubicular* region is characterized by an already well formed cortical plate, which, however, is strongly narrowed as compared with the *isocortex*. At this stage of development it seems to present the homologue only of the upper portion of the definitive *presubicular* region (*Psb*), while the lower portion of the latter is formed only later by further condensation of the *stratum intermedium* of the wall of the brains. At the 80 mm. stage a well defined superlamination of the *isocortical* plate on Ammon's plate is seen in the region of the

presubiculum superius (fig. 2, *PA*), each plate presenting a wedge-shaped narrowing. Hence the upper portion of the presubiculum superius forms the continuation of the isocortical plate, and the lower portion, the continuation of Ammon's plate; the two plates are separated from each other by a clearly defined, light intermediate layer, or stratum dissecans (*Diss*²). The splitting in presubiculum inferius occurs at the 130 mm. stage or somewhat earlier; at the 80 mm. stage the cortical

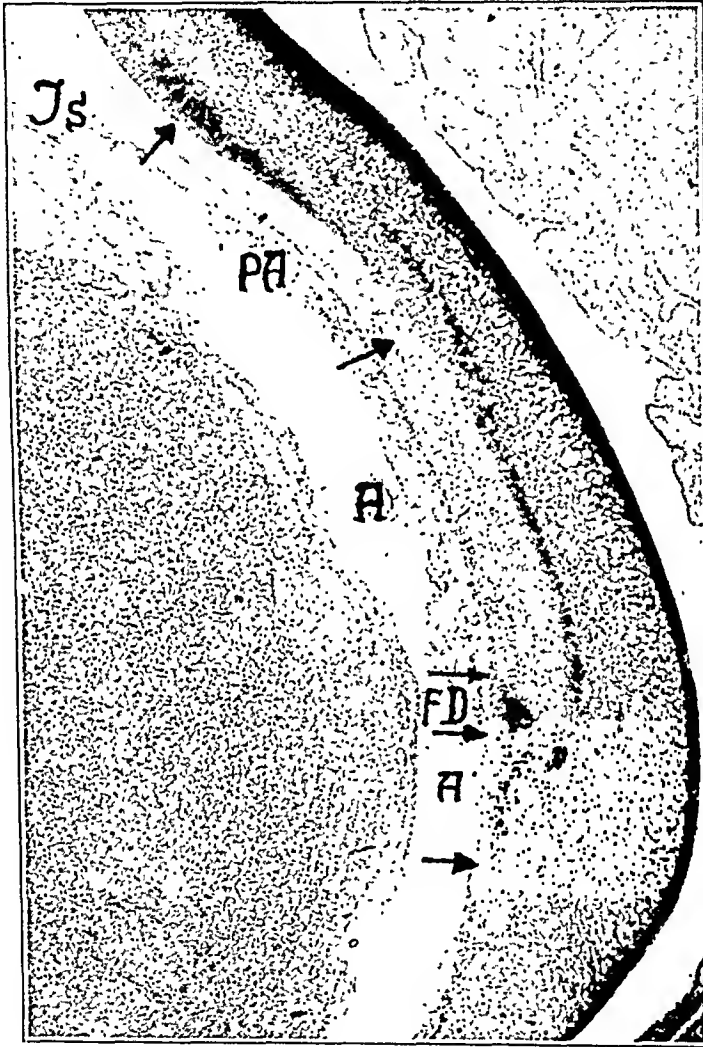


Fig. 2.—Stage, 80 mm. *A* is archicortex (subiculum and cornu ammonis); *FD*, fascia dentata; *Is*, isocortex, and *PA*, periarchicortex (here, presubiculum superius).

plate of the presubiculum inferius, which is very wide, but rarefied in its deeper part, exhibits an immediate transition *in toto* into Ammon's plate. In later stages the inner part seems to show rarefaction and merging with Ammon's plate, whereas the outer part exhibits condensation and separation from the inner part through formation of a stratum dissecans.

Thus, the process of splitting in the region of the presubicular region arises only secondarily and presents the result of comparatively late ontogenetic development. It is to be strongly emphasized, however, that the process of splitting follows here a quite definite direction, separating cortical plates which differ profoundly from each other, according to their genetic character.

The presubicular region is situated in the immediate neighborhood of the archicortical zone and surrounds it almost completely. It is, accordingly, represented not only by the temporal but also by the retrosplenial, supracallosal and subgenual parts. However, its typical

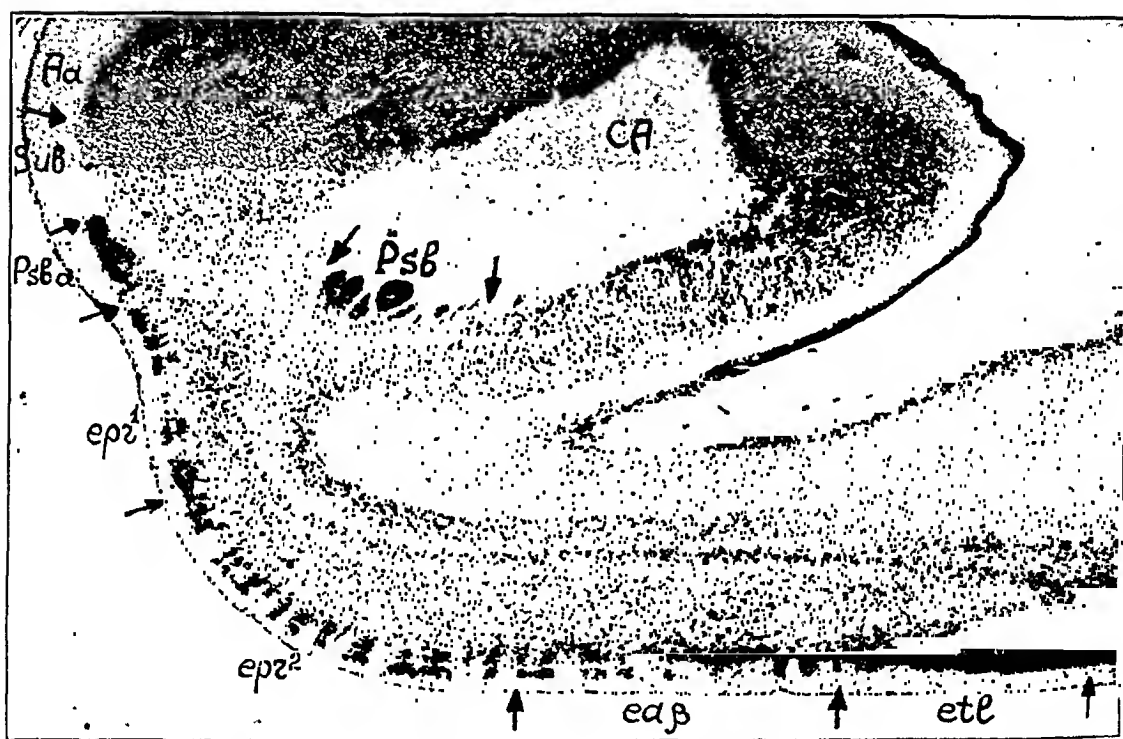


Fig. 3.—Stage, 180 mm. *Aa* + *CA* indicate cornu ammonis; *epr*¹ (only *Diss*²) and *epr*² (*Diss*¹ + *Diss*²), subregion entorhinalis propria; *eaβ* (only *Diss*¹) is subregion entorhinalis anterior; *etl*, subregion entorhinalis transgrediens lateralis; *Psb a*, presubiculum anterius; *Sub*, subiculum.

structure is maintained throughout the process of development only in the temporal part. Here the upper portion (external [*ext*] and intermediate [*m*] layers) presents a granular character even in the adult, and the region maintains a typical subdivision into two structures, *Psb 1* and *Psb 2*, which show fusion into a single formation, *Psb a*, only in their oral part (fig. 3, *Psb a*). The retrosplenial part exhibits at late stages and in the adult brain four clearly differentiated formations: *Psb 1*, *Psb 1a*, *Psb 2a* and *RS*. Of these formations, only *Psb 1* has a typical presubicular structure (granular upper portion); other forma-

tions show pyramidization either of the superficial part of the upper portion (*Psb 1a* and *Psb 2a*) or of the entire upper portion (*RS*). However, here also one must admit the presence of true presubicular formations, as evidenced by the course of their evolution: In early stages the upper portion of the calcarine trunk is occupied in its oral part by typical presubicular formations and in late stages, as well as in the adult, by formations *Psb 2a* and *RS*.

In the supracallosal and subgenual parts the structure of the presubicular region is strongly modified: Its upper portion shows complete pyramidization, and in the oral part the subdivision into formations *Psb 1* and *Psb 2* becomes effaced, the region presenting even in early stages a single formation—*Psb 3a*. Nevertheless, even the subgenual part of the presubicular region, the characteristic structure of this region, remains for the most part clearly pronounced; the cortical plate of the archicortex, exhibiting large cells (here of the tenia tecta), penetrates into the deeper portion and on it is superimposed the external plate of the presubiculum, which presents a quite different, though nongranular structure.

The entorhinal region already shows splitting of the cortical plate at the 55 mm. stage, e. g., earlier than does the presubicular region (*Psb*). The stratum dissecans appears here first in the deeper part of the cortical plate; during further development (fig. 4, *cp*) it becomes more superficially situated (*Diss*¹), owing to increase in the width of the cortex through apposition (from below). The deep stratum dissecans, corresponding to the stratum dissecans of the presubiculum (*Diss*²), appears in the entorhinal region only later, and not throughout the whole region. The great significance of the difference between the two strata dissecantia is to be strongly emphasized. In the presubicular, as well as in the entorhinal, region the cortical plate is subdivided into three chief layers: external (*ext*), intermediate (*m*) and internal (*int*), only the internal one showing transition into Ammon's plate. The stratum dissecans of the presubiculum (*Diss*²) separates Ammon's plate from the upper layers (external and intermediate) of the periarchicortical zone, which correspond to the isocortical plate and overlie Ammon's plate, while the deep stratum dissecans (*Diss*¹), in a well defined form encountered only in the entorhinal region, is situated within the layer *m*. The difference between the strata dissecantia in respect to their level is clearly seen in figure 4 (at the 150 mm. stage) (*Psb 2* and *cp*), and is also evident in formations in which the strata dissecantia are both present. (fig. 3, *ep*²).

In addition to these chief strata dissecantia, the stratum dissecans externum (*Diss*^{ext}) is seen in some entorhinal formations, either subdividing the external layer (*ext*) into two sublayers or separating the external layer (*ext*) from the intermediate layer (*m*). A quite typical sublayer (stratum interlaminare), formed of large cells, is situated

between the two chief strata dissecantia, *Diss*¹ and *Diss*² (fig. 3, *epr*²). This sublayer is also clearly seen in many formations in which only one stratum dissecans is present (fig. 3, *eaβ*). In such cases it acquires considerable importance for adequate qualification of this stratum dissecans: The stratum dissecans situated over the stratum interlaminare



Fig. 4.—Stage, 150 mm. Here *ep* is subregion entorhinalis posterior (only *Diss*¹); *Psb 1* and *Psb 2* indicate regio presubicularis (*Psb 2*, only *Diss*²); *Pse*, parasubiculum.

is to be considered as stratum *Diss*¹, and the stratum dissecans, situated under this layer, as stratum *Diss*².

The complete (the ideal, so to speak) stratification of the entorhinal region can be formulated as follows: *ext* (subdivided into sublayers by

stratum *Diss*^{ext}; *m* (+ stratum *Diss*¹ + stratum interlaminare); stratum *Diss*²; internal layer (*int*).

In reality, stratification in various entorhinal formations presents deviations of one sort or another from this ideal type, owing to which the entorhinal region may be subdivided at relatively early stages of development into six subregions on the basis of quite definite peculiarities. It is anteriorly, posteriorly and laterally separated from the isocortex by intermediate subregions: anterior (*eta*), posterior (*etp*) and lateral (*etl*). The chief part of the region consists of three main subregions: the posterior (*ep*), the middle, or regiopropria or media (*tpr*), and the anterior (*ea*). The entorhinal region is separated from the presubicular region by the parasubicular formation (fig. 4, *Psc*) and from the periamygdalar region by the formation *epm*, characterized by the disappearance of the stratum interlaminare (*int*) and the maintenance of the typical *ext Diss*^{ext} *m* formation.

The subregion *etp* differs in early stages from the isocortex by some rarefaction in sublayer *m*, and in late stages by discontinuation of sublayer *ext* and by the absence of layer IV. At the same time, it cannot be referred to the quite typical entorhinal region, owing to the absence of the strata dissecantia.

The subregion *ep* is entirely typical at all stages because of the presence of a well defined deep stratum dissecans, *Diss*¹ (fig. 4, *ep*).

The subregion *epr* is characterized in early stages by the presence of the so-called limes duplex in the site of transition to the isocortex (fig. 3, *eaβ* and *etl*), and by the presence of stratum *Diss*² in the late stages (from 180 mm. to the adult), the latter being absent in all other entorhinal subregions. Only stratum *Diss*² is present in the formation *epr*¹ and both stratum *Diss*¹ and stratum *Diss*² are seen in formation *epr*² (fig. 3, *epr*¹ and *epr*²). In early stages (130 to 150 mm.) the formation *epr*¹ is characterized by the absence of true strata dissecantia; only rarefaction of the *m* layer (pseudodissecans) is to be seen, while in the formation *epr*² on stratum *Diss*¹ is clearly defined.

Subregion *ea* is characterized by the presence of stratum *Diss*¹ alone (fig. 3, *eaβ*) and is relatively early subdivided into two quite distinct parts: internal (*ea*¹) and external (*ea*). At later stages, each of these parts is differentiated into separate formations according to more special features: *ea* into *eaα*, *eaβ* and *eaγ*; and *ea*¹ into *ea*^{1α}, *ea*^{1β}, *ea*^{1γ} and *ea*^{1δ}.

The anterior intermediate subregion, *eta*, is subdivided into formations *eta*¹ and *eta*²; between these formations and the prepiriform region is situated the *p per* formation, where the layer *ext* presents a quite typical aspect for the region *Pp*, but where the cortical plate, at the same time, shows the presence of stratum *Diss*¹ and the internal layer (*int*). The intermediate formation *eti* forms a transition of the subregion *eta* into the insular (perisemicortical) region.

The intermediate formations in this region (epr^0 and epr^{00} , between the subregions ep and epr ; the aforementioned formations Pse and epm , and so forth), as well as in other regions, are numerous.

One general principle prevails throughout the entire process of ontogenesis, which I shall designate as the principle of intermediate formations: Between formations showing strong structural or, especially, genetic differences, one is sure to detect intermediate formations, the structure of which bears to a certain degree a transitional character, these formations being, however, sharply (*saarscharf*) separated from each other. This principle forms also the basis of the division of the cerebral cortex into three main territories, of which we consider the cortex intermedius structurally and genetically an area of transition between the cortex completus and the cortex incompletus.

The lateral intermediate subregion, etl , separating the central entorhinal subregions from the isocortex throughout almost its entire extension, is similar in the early stages to the subregion etp (rarefaction of the m layer). In later stages a wedge-shaped darkening of the m layer in the direction of the isocortex (fig. 3, etl) is characteristic of the greater middle part of subregion etl . This wedgelike shape is clearly seen in the adult brain also, though not so strongly pronounced. As regards other features of the subregion etl , it should be noted that layer ext possesses here no papillar structure and the cortical plate fails to show a true stratum dissecans, differing in this respect from adjacent entorhinal formations, and that, on the other hand, it presents (in contrast to the isocortex) discontinuity in structure of layer ext and absence of layer IV.

On the whole, Ammon's plate within the entorhinal region is separated from the isocortical plate as distinctly as it is within the pre-subicular region. This separation is effected by the presence of stratum $Diss^2$ (formations epr^1 and epr^2 , fig. 3) or by the presence of stratum interlaminare (formation $ea\beta$, fig. 3). Superlamination is particularly clear here, as represented by limes duplex, e. g., by free termination of Ammon's plate, which disappears in the subjacent white matter at the border of the entorhinal region (fig. 3, $ea\beta-etl$). It is true that limes duplex becomes effaced in the late stages, as a result of continuous migration of neuroblasts into the isocortex, where they subsequently form its extreme layer, merging with the internal layer of the entorhinal cortex. Thus, the extreme internal layer of the isocortex seems to correspond here to Ammon's plate—essentially layer VI of the isocortex, the fifth one corresponding in part to stratum $Diss^2$ (V b) and in part to stratum interlaminare (V a). It must, however, be emphasized that this conformity arises only secondarily at a comparatively late stage of ontogenesis.

The perisemicortical zone (insular intermediate region) is in some respects similar to the periarchicortical one: that is, it also consists of a number of formations (*ii*, *ia*, *il*, *ii*², *ii*¹, *ii*⁰) which effect a successive, though interrupted, transition (these formations are sharply separated from each other) from the cortex incompletus (here semicortex) to the cortex completus. The formation *ii*, which is the one nearest the isocortex, is characterized in early stages by a wedge-shaped widening of the cortical plate in the direction of the isocortex, while the formation *ii*⁰, which is the one nearest the semicortical zone, presents strong rarefaction of the cortical plate (fig. 6). In the adult the formation *ii*⁰ is far from being so rarefied, but it is still well differentiated from surrounding formations by its looseness and extreme effacement of stratification.

Other, and quite essential, features are also concerned in the similarity between the insular intermediate layer and the entorhinal region, a similarity which is in full conformity with our concept of unification of the perisemicortical and the periarchicortical zone as the cortex intermedius and with our subdivision of the entire cerebral cortex into three, and not into the traditional two, main territories. A wedge-shaped transition of the isocortex into intermediate formations (figs. 3 and 5, *etl* and *ii*) occurs in both cases. The structure of the stratum interlaminae, so typical of entorhinal formations, is quite similar to the structure of the intermediate layer (*Va* of some authors) of the insular formations *ii*², *il* and, in part, *ii*. Finally, the typical splitting of the cortical plate in the entorhinal region, revealing its transitional character, may, with full justification, be compared to the presence of the claustrum in the insular region.

As a matter of fact, our ontogenetic investigations have disclosed that the claustrum cannot be considered either as a derivative of the cortical plate, as some believe, or as a formation genetically similar to the striatum or to the nucleus amygdalae, as others hold; it is to be regarded, rather, only as an intermediate formation. Whereas the striatum and the amygdalar region are immediately connected with the matrix, and the cortical plate presents in the region of the isocortex and archicortex an accumulation of neuroblasts on the surface of the end brain, separated from periventricular cell masses, the claustrum is separated from the matrix and, at the same time, represents the result of an accumulation of neuroblasts, the chief mass of which failed to reach the cortical plate in the process of their migration and were arrested a certain distance between the cortical plate and the striatum. In the early stages the claustrum is actually involved in a dense, diffuse accumulation of neuroblasts (zone *R* according to our terminology; fig. 5), which is continuous with the cortical plate. However, there is

no reason to regard zone *R* (continuing into the nucleus amygdalae immediately!) as the internal layer of the cortical plate, because this zone, like the intermediate layer (*z*) in the isocortical region, represents only

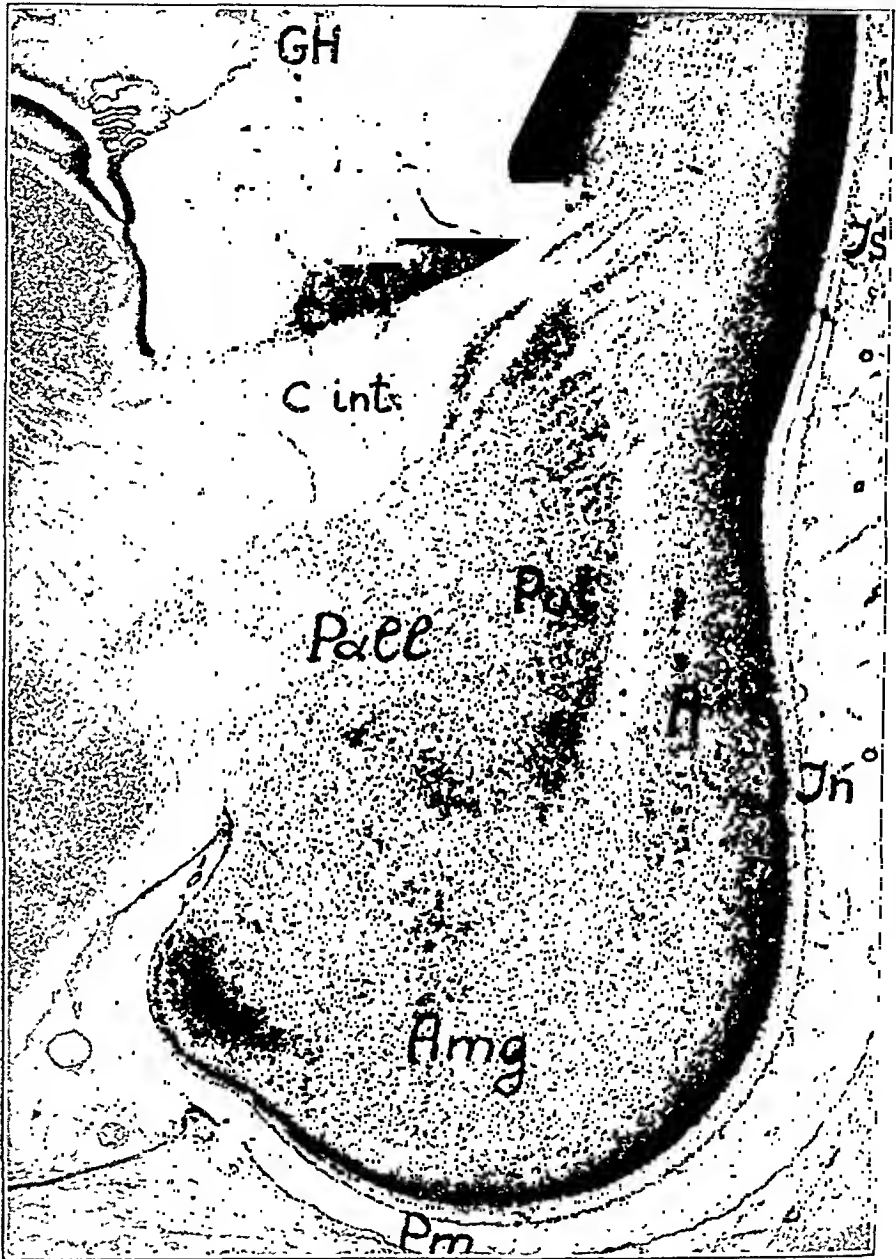


Fig. 5.—Stage, 55 mm. *Amg* indicates nucleus amygdalae; *C int*, internal capsule; *Gh*, Hügel's ganglion; *In*, insular region; *Is*, isocortex; *Pall*, pallidum; *Pm*, periamygdalar region; *Put*, putamen; *R*, zona *R*, including claustrum and continuing into nucleus amygdalae.

a zone of migration of neuroblasts, and by no means a zone of their stabilization, as is to be expected of a true cortical plate.

Correlations in the region of the allocortical zones *sensu strictiori* are considerably simpler than those in the region of the cortex intermedius.

The archicortical zone is already differentiated in an early stage into the subiculum (*Sub*), the cornu ammonis (*CA*) and the fascia dentata (*FD*), while the cornu ammonis is divided into sectors h^1 to h^6 ; all these formations (except the fascia dentata [*FD*]) continue, showing structural modifications, over the corpus callosum (tenia tecta). The subdivision into distinct formations is effaced orally, in the supracallosal and subgenual portions. The same correlations are also seen in the adult brain. This stability of differentiation into separate formations, together with the stability of general structural features, is characteristic of the



Fig. 6.—Stage, 130 mm. *Cl*, claustrum; *D²*, regio diagonalis; *ii°* and *ii*, perisemicortical formations; *Pp¹* + *Pp²*, regio prepiriformis; *T¹* and *T²*, tuberculum olfactorium.

archicortex, in contrast to the cortex intermedius and, particularly, with the entorhinal region.

The semicortical regions—the tuberculum olfactorium (fig. 6, *T*) and the regio diagonalis—are characterized by still greater stability and in all the stages reveal differentiation into typical formations, T^1 and T^2 , D^1 and D^2 (fig. 6).

The changes in the periamygdalar region are more considerable. In early stages it consists of four formations, elongated orocaudally and parallel to each other: *Pe*, *Pml²*, *Pml¹* and *Pmm*, which show transitions into the prepiriform region through intermediate formations *Ppl²*,

*Ppl*¹ and *Ppm*. The same subdivision is maintained at later stages in the caudal part, while in the oral part *Pml*² and *Pml*¹ no longer exhibit differentiation and show transition into a common formation *Pml*³, the last passing into a common intermediate formation, *Ppl*, which no longer shows subdivision into *Ppl*¹ and *Ppl*², as it does in early stages.

The problem of development of the periamygdalar cortex is closely connected with the problem of the genesis and nature of the nucleus amygdalae.

According to our investigations, the amygdalar complex is not to be considered as a modified and thickened part of the temporal cortex which has separated from the latter and embedded itself in the depth of the subcortex, but it is also inadmissible to contrast it with the periamygdalar formations. The entire process of development obviously shows that the periamygdalar cortex belongs to the cortex semiseparatus in our sense, e. g., to the zone where the cortical plate shows incomplete separation from the periventricular cell masses—in our particular case, from the nuclei of the amygdala, which fully belong to these masses (fig. 5).

The prepiriform region presents similarity to the insular region in that here, also, the cortical plate is situated over the claustrum (fig. 6, *Pp*); however, correlations show here much more stability in the process of evolution than in the insular region, and its structure presents essential differences both with respect to the marginal layer and to the cortical plate. Beginning from 130 mm. (or somewhat earlier) and covering the whole process of further development, this region shows subdivision into four formations: *Pp*¹, characterized by a compact, narrow and tortuous cortical plate; *Pp*², which occupies the gyrus olfactorius lateralis and is characterized by a very wide layer I and a rarefied cortical plate, and *Pp*^{2a} and *Pp*^{2β}, presenting a transition from the chief formation, *Pp*², to the chief formation, *Pp*¹. A similar subdivision is seen in the prepiriform region of the adult brain also.

Important is the problem of conformity of the development of the allocortical and periallocortical formations, or the cortex incompletus and the cortex intermedius, respectively, with the fundamental biogenetic law. The process of development of the semicortical zone is in full accordance with this law. This region, which is phylogenetically the oldest (paleocortex) and closest to the oldest type of end brain structure (presence of periventricular cellular masses alone), is, at the same time, the first to develop in the process of ontogenesis. Correlations in the archicortical zone are much more complex. Unexpectedly, the cortical plate is here differentiated not earlier, but later, than in the decidedly phylogenetically younger isocortical plate (neocortex). However, the development of the archicortical or Ammon's zone is completed earlier than that of the isocortex, which means that on the whole its development presents a considerably shorter course than that of the isocortex.

The differentiation of cellular elements generally starts in the cortex incompletus and the cortex intermedius earlier than in the cortex completus, though this varies in different regions. Here, also, as in the isocortex, the initial rate of evolution by no means always conforms with the definitive size of the corresponding cells.³ Ammon's zone is of particular interest in this respect. Here, the cells in formation h^2 begin to increase in size much earlier than the cells in formation h^4 and h^5 , although the cells in formation h^4 and h^5 are in the adult but slightly smaller than those in formation h^2 .

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PHYSIOLOGY AND THERAPY OF CONVULSIVE DISORDERS

I. Effect of Anticonvulsant Drugs on Electroshock Seizures in Man

JAMES E. P. TOMAN, Ph.D.

S. LOEWE, M.D.,

AND

LOUIS S. GOODMAN, M.D.

SALT LAKE CITY

THE EFFECTS of drugs on various properties of electroshock seizures in experimental animals have been described in previous communications from this laboratory.¹ Many anticonvulsant drugs in nontoxic doses have been found to modify the seizure pattern, usually by shortening or abolishing the tonic phase. A simple and quantitative method of assay of anticonvulsant drugs has been developed on the basis of this selective action.¹¹ Of the more widely used antiepileptic agents, diphenylhydantoin, phenobarbital and "tridione" (trimethadione) rank

From the Departments of Physiology and Pharmacology, University of Utah School of Medicine.

This investigation was made under the auspices of a grant in aid of research from the United States Public Health Service.

1. (a) Goodman, L. S.; Swinyard, E. A., and Toman, J. E. P.: Laboratory Technics for the Identification and Evaluation of Potentially Antiepileptic Drugs, *Proc. Am. Federation Clin. Research* 2:100-101, 1945; (b) Studies on the Anticonvulsant Properties of Diphenylhydantoin, *Federation Proc.* 5:180, 1946; (c) Effects of *b* (+) Glutamic Acid and Other Agents on Experimental Seizures, *Arch. Neurol. & Psychiat.* 56:20-29 (July) 1946. (d) Goodman, L. S., and Toman, J. E. P.: Experimental Indices for Comparing the Efficacy of Compounds with Anticonvulsant and Antiepileptic Properties, *Federation Proc.* 4:120, 1945. (e) Goodman, L. S.; Toman, J. E. P., and Swinyard, E. A.: Anticonvulsant Properties of Tridione: Laboratory and Clinical Investigations, *Am. J. Med.* 1: 213-228 (Sept.) 1946. (f) Swinyard, E. A., and Goodman, L. S.: Laboratory Assay of Anticonvulsant Potency of Some Hydantoinates, *Federation Proc.* 5:205-206, 1946. (g) Swinyard, E. A.; Toman, J. E. P., and Goodman, L. S.: The Effects of Cellular Hydration on Experimental Electroshock Convulsions, *J. Neurophysiol.* 9:47-54, 1946; (h) The Effects of Body Water and Electrolyte Shifts on Experimental Convulsions, *Federation Proc.* 5:205, 1946. (i) Toman, J. E. P.; Swinyard, E. A., and Goodman, L. S.: Some Properties of Maximal Electroshock Seizures, *ibid.* 5:105, 1946. (j) Properties of Maximal Seizures, and Their Alteration by Anticonvulsant Drugs and Other Agents, *J. Neurophysiol.* 9:231-239, 1946

as named in decreasing order of effectiveness when examined by this method.

It would seem important to determine whether the pattern of electroshock seizures in man can be modified by anticonvulsant drugs in doses known to be clinically effective in epilepsy. Such information might help to elucidate the mechanism of action of drugs in control of convulsive disorders. The common use of electroshock seizure therapy of certain psychiatric disorders provides an opportunity for such observations on nonepileptic subjects. Although a number of investigators have studied the ability of barbiturates, diphenylhydantoin and other agents to raise the electroshock seizure threshold in man,² only desultory attention has been paid to the modification of the seizure pattern by these drugs. It has been observed^{2b} and confirmed^{2d} that patients given premedication with diphenylhydantoin have a greater than normal incidence of atypical seizures. A brief comment on the ability of diphenylhydantoin to shorten the tonic phase in man^{2b} antedates similar observations on animals.³

The present communication is concerned chiefly with the relative ability of some commonly used anticonvulsant drugs to alter the seizure pattern in patients receiving electroshock therapy. The work was undertaken in order to extend our investigations from animals to man and to examine the possibility of developing a simple method of assay of the action of anticonvulsant drugs in man.

MATERIALS AND METHODS

The Offner and Rahm 60 cycle, alternating current instruments were used for electroshock therapy. The strength of the stimulating current ranged from 500 to 750 milliamperes and the duration of the stimulus from 0.2 to 0.4 second. The various components and the total duration of each seizure were timed to the nearest second. Control

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observations were made on 22 male and 14 female adult psychiatric patients. Of these, 15 men and 7 women were chosen for a study of the effects of drugs on the seizure pattern. The following agents and dosage schedules were used:

1. Diphenylhydantoin sodium ("dilantin sodium"): 0.4 to 0.8 Gm. daily for four days.
2. Phenobarbital: 0.3 to 0.4 Gm. daily for one to three days.
3. "Tridione"⁴ (trimethadione; 3, 5, 5-trimethyloxazolidine-2, 4-dione): 2.4 to 3.6 Gm. daily for two to three days.
4. Sodium bromide: 6.0 to 9.0 Gm. daily for one week. The serum bromide level was determined just prior to the electroshock test.
5. "Mebaral" (*N*-methyl, 5-ethyl, 5-phenyl barbituric acid): 0.8 to 1.2 Gm. daily for three days.
6. "Mesantoin"⁵ (*N*-methyl, 5-phenyl, 5-ethyl hydantoin): 0.4 to 0.6 Gm. daily for four days.

It was intended that the lower dose of each drug should fall within the customary range for antiepileptic medication and that the higher dose should exceed this range.

RESULTS

Control Seizures.—A total of 67 electroshock seizures were observed in 36 patients without prior administration of drugs. The initial control seizures elicited in these patients are presented graphically in figure 1, in which the results are arranged in order of decreasing duration of the tonic phase. The total duration of the seizure is calculated from the time of onset of the tonic phase because of the great variation in the latent period⁶ (mean, five seconds; range, one to thirty seconds). Calculated in this way, the total duration of the seizure is the most constant property of electroshock convulsion in man (mean, 36 seconds; range, 27 to 43 seconds; standard deviation, 4 seconds); it does not appear to be related either to the latent period or to the duration of the tonic phase. The duration of the tonic phase was more variable

4. "Tridione" was supplied by Dr. R. K. Richards, of the Abbott Laboratories, North Chicago, Ill.

5. "Mesantoin" was supplied by Mr. S. M. Fossel, Sandoz Chemical Works, Inc., New York.

6. In animal experiments, the duration of the latent period is inversely related to the excess of current above threshold and approaches a limiting value of two seconds.¹¹ Long latent periods in electroshock seizures in man probably indicate that the current did not greatly exceed threshold.^{2c} In the present series of patients, it was not found feasible to use intensities of current as far above threshold as those employed to insure maximal seizures in animals.¹¹

(mean, 13 seconds; range, 4 to 24 seconds; standard deviation, 4 seconds). Although an extensor component of the tonic phase comparable to that seen in experimental animals¹¹ was demonstrable in most patients, the sequence of postural changes within the tonic phase was rather variable, even in the same patient during consecutive trials. Therefore no attempt has been made to subdivide the tonic phase in this report. No significant sex difference was observed in the pattern or duration of seizures.

In figure 2 are shown two consecutive control seizures in each of 11 patients. The threshold for tonic-clonic seizures was definitely increased in only 2 patients on second trial. The pattern and duration

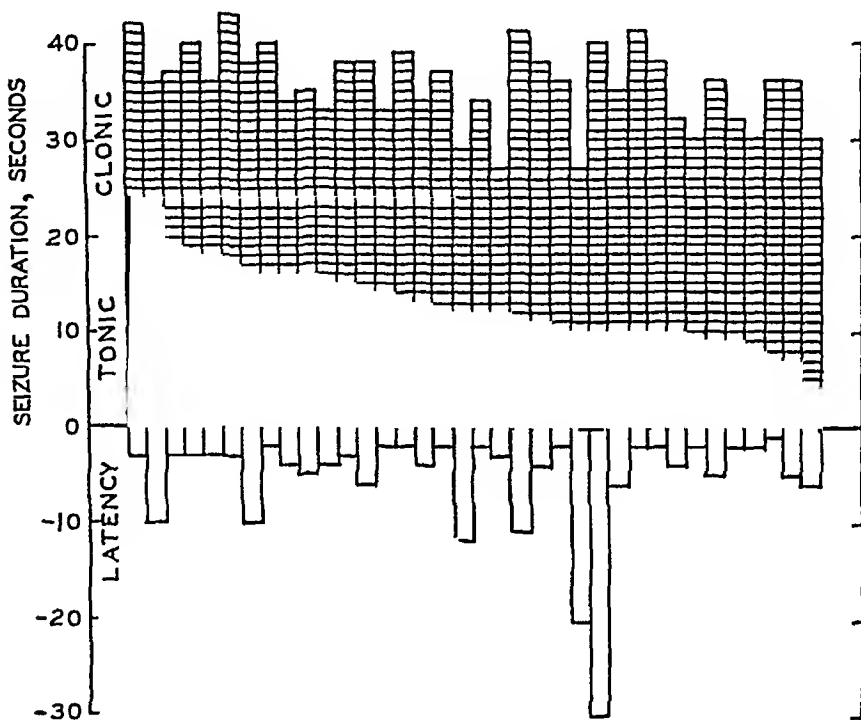


Fig. 1.—Pattern and duration of initial control electroshock seizures in 36 patients, arranged from left to right in order of decreasing duration of the tonic phase. In this figure, and in the accompanying figures, the duration of seizures was calculated from the onset of the tonic phase, which is shown in solid black. The clonic phase is represented by cross hatching. The latent period is timed from administration of the stimulus to onset of the tonic phase and is shown by open rectangles below the base line. The electroshock current ranged from 500 to 700 milliamperes, and the duration of stimulation, from 0.2 to 0.4 sec.

of seizures in these and in subsequent control trials provided a basis of reference for the effects of drugs.

In classifying electroshock seizure patterns in man, the following difficulty in interpretation was frequently encountered. After receiving a shock which fails to produce a tonic-clonic seizure, the patient often exhibits apnea, signs of confusion and automatism for a minute or

longer. Such activity resembles a psychomotor seizure or ictal automatism,⁷ but has been given various names, such as "petit mal" or "subconvulsive response."^{2c} That this phenomenon is indeed a seizure is attested by the following observations: 1. If a second shock of the same intensity and duration of current as the original is given within about fifteen seconds of the "missed shock," a major tonic-clonic seizure usually develops. We have found in experimental animals that true summation of inadequate stimuli can occur only with stimulus intervals of two seconds or less; however, if the first shock produces only electroencephalographic evidence of seizure activity, a second shock of the same intensity given at any time during such activity can then cause the appearance of an overt "clinical" seizure.⁸ 2. Even without a second shock the patient may ultimately exhibit

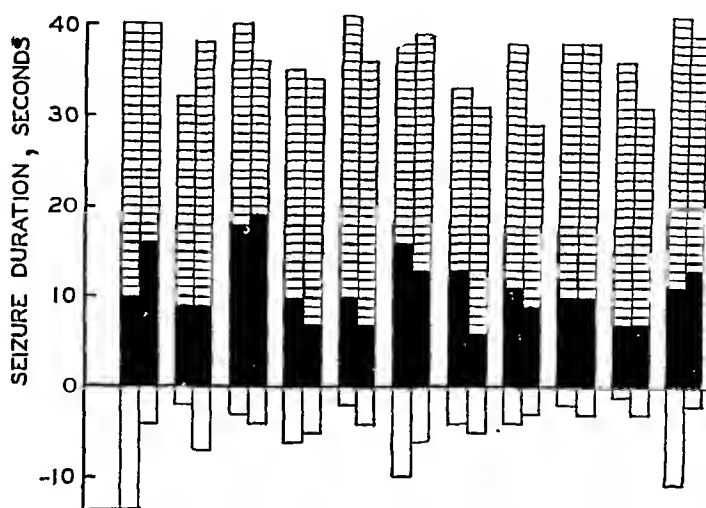


Fig. 2.—Variability of control electroshock seizures elicited in 11 patients. Each pair of columns represents the pattern and duration of seizures occurring during two consecutive treatments, given two days apart. This graph is to be compared with subsequent figures showing effects of drugs.

a major seizure. Latent periods as long as ninety seconds have been observed; other instances of long delay are seen in figure 1. 3. If the second shock is withheld for several minutes after a "petit mal" seizure, the duration and intensity of current must often be considerably increased in order to produce a tonic-clonic seizure. In accordance with our observations on animals, this may indicate postseizure refractoriness following a "subclinical" seizure discharge in the electroencephalogram. Such a subclinical electroencephalographic discharge in

7. Penfield, W., and Erickson, T. C.: *Epilepsy and Cerebral Localization*, Springfield, Ill., Charles C Thomas, Publisher, 1941.

8. Toman, J. E. P.; Swinyard, E. A., and Merkin, M.: Unpublished data.

animals resembles the pattern of spontaneous human psychomotor seizures but is quite unlike a petit mal record.

Because of these considerations, we have preferred to classify any electroshock response consisting of apnea, confusion and automatism as a psychomotor seizure.

Modification of Seizures by Drugs.—For convenience in analyzing the action of a drug, only three types of seizures were considered: (a) psychomotor seizures (as previously described); (b) clonic seizures (with no initial tonic phase), which were never observed in patients not receiving medication; (c) tonic-clonic seizures (typical electroshock convulsions with an initial tonic phase), which could always be elicited

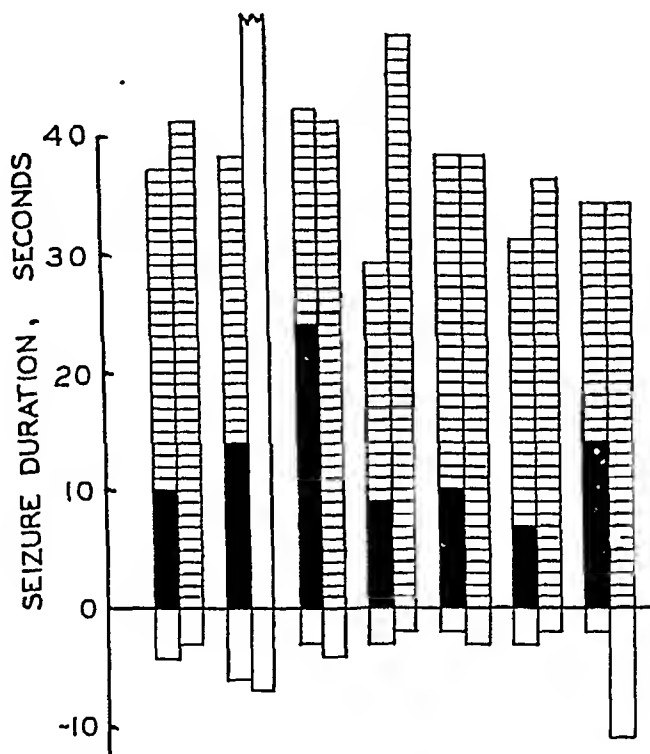


Fig. 3.—Effects of diphenylhydantoin on the pattern and duration of electroshock seizures in 7 patients. The first column in each pair represents the control seizure; the second, the seizure after a course of diphenylhydantoin medication. Observe that the tonic phase is abolished in all cases. The open column in the second pair from the left denotes a psychomotor seizure of long duration. The first 3 patients (starting at the left of the figure) received 0.4 Gm. of diphenylhydantoin sodium daily for four days; the next 3 patients, 0.6 Gm. daily, and the remaining patient, 0.8 Gm. daily.

in patients without medication within the range of intensity of the current of the electroshock apparatus.

No attempt was made to measure the threshold for minimal (psychomotor) seizures. Rather, the ability of each drug to prevent the appearance of typical tonic-clonic seizures was taken as the criterion of anticonvulsant action.

Diphenylhydantoin: Of 7 patients receiving diphenylhydantoin and retested with the control electroshock current and duration, the seizures were clonic throughout in 3 and psychomotor in 4. When the electroshock current and duration were increased with the latter 4 patients, clonic convulsions occurred in 3. The fourth patient again exhibited only a psychomotor seizure, but a facial clonic component was present. Figure 3 illustrates these results. Diphenylhydantoin consistently abolished the tonic phase of the convulsions. In the doses employed the drug caused no toxic effects.

Phenobarbital: Figure 4 illustrates the results obtained with 7 patients receiving phenobarbital. Two patients receiving the higher

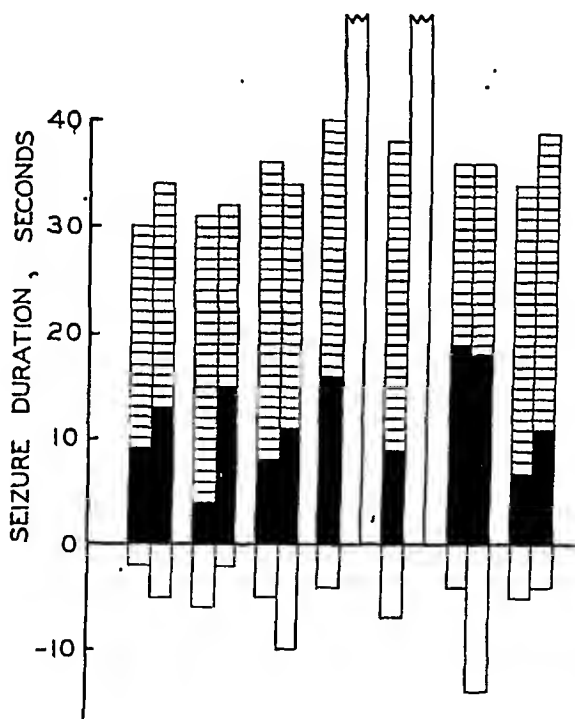


Fig. 4.—Effects of phenobarbital on the pattern and duration of electroshock seizures in 7 patients. The first column in each pair represents the control seizure; the second, the seizure after a course of phenobarbital medication. The first 3 patients (starting at the left of the figure) received 0.3 Gm. of phenobarbital for one day; the remaining 4 patients, 0.4 Gm. daily for three days.

dose reported that the drug caused vertigo and sedation, and in these 2 subjects only psychomotor seizures of long duration were elicited despite an increase in stimulating current. The remaining 5 patients did not show any toxic or depressant effect of phenobarbital. Tonic-clonic seizures were obtained in 2 of these 5 patients only after the stimulating current was increased. In the remaining 3 patients, such seizures were obtained with the intensity of current and duration of

stimulus used in the control seizure. The results indicate that after nontoxic doses of phenobarbital a tonic-clonic seizure may still be elicited, although an increase in the electroshock current or duration may be required.

"Tridione" (Trimethadione): Figure 5 illustrates the results obtained with 8 patients receiving trimethadione. None complained of toxic effects from the doses employed. The drug did not increase the threshold for tonic-clonic seizures.

Sodium Bromide: The results of administration of sodium bromide for 9 patients are given in figure 6. The serum bromide levels at the

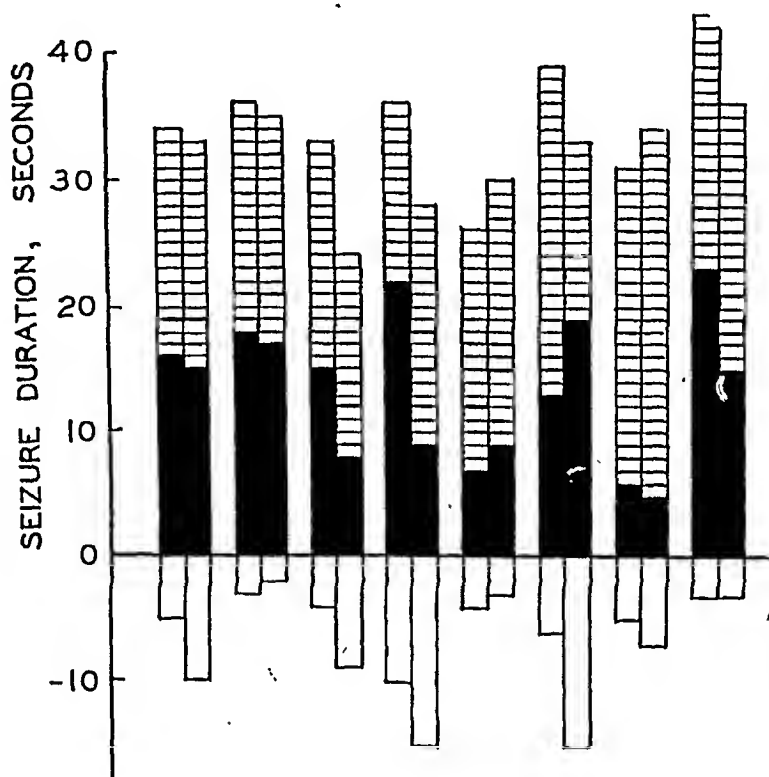


Fig. 5.—Effect of "tridione" (trimethadione) on the pattern and duration of electroshock seizures in 8 patients. The first column in each pair represents the control seizure; the second, the seizure after a course of trimethadione medication. The first 4 patients (starting at the left of the figure) received 2.4 Gm. of trimethadione daily for two days; the next patient, 3.6 Gm. daily for two days, and the last 3, 3.6 Gm. daily for three days.

time of the electroshock observations ranged from 135 to 235 mg. per hundred cubic centimeter (13 to 23 milliequivalents per liter of bromide). Nausea and an acneform rash were observed in 1 patient and sedation in 3 others. These signs bore no definite relation to the serum bromide level. The threshold for tonic-clonic seizures was definitely increased in 3 of the patients with toxic symptoms and in 1 other. In 2 of these patients the tonic-clonic seizures could be obtained with the maximum

intensity of current and duration of shock available, but the tonic phase was shortened by more than 50 per cent as compared with previous controls. In a third patient only a psychomotor seizure was obtained, and in a fourth the severest convulsion elicited was purely clonic throughout.

"Mebaral" (*N*-methyl, 5-ethyl, 5-phenyl barbituric acid): The results of medication with "mebaral" are illustrated in figure 7. In 6 patients receiving the lower dose of "mebaral" (0.8 Gm. daily for three days) there was no evidence of modification of the seizure pattern or of elevation in threshold for tonic-clonic seizures. No toxic signs were observed. In 3 other patients receiving 1.2 Gm. of "mebaral" daily

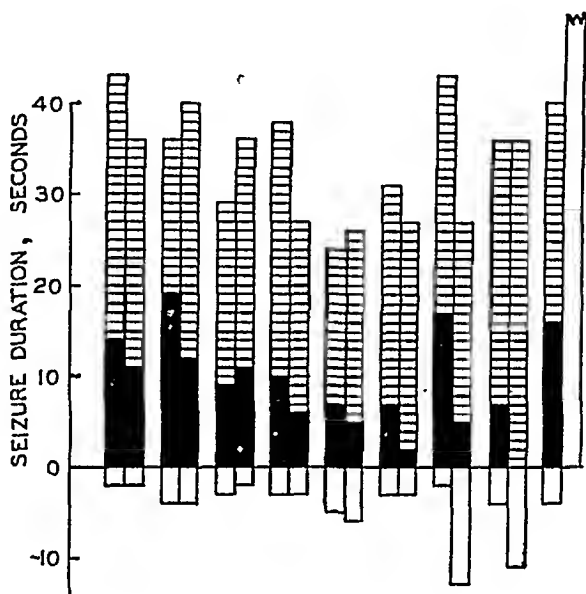


Fig. 6.—Effect of sodium bromide on the pattern and duration of seizures in 9 patients. The serum bromide levels for these patients ranged from 135 to 235 mg. per hundred cubic centimeters (13 to 23 milliequivalents per liter of bromide). The values for individual patients (left to right) were 235, 208, 172, 135, 170, 160, 200, 197 and 164 mg. per hundred cubic centimeters.

for three days there was definite sedation. Only psychomotor seizures could be obtained in 2 of these 3 patients.

"Mesantoin" (*N*-methyl, 5-phenyl, 5-ethyl hydantoin): Of the 4 patients receiving 0.4 Gm. of "mesantoin" daily for four days, 1 complained of vertigo and was found to have a slight elevation in temperature. Several weeks later this patient was placed under treatment with the higher dose of "mesantoin," without untoward effects. None of the 4 patients showed alteration in type of seizures or elevation in threshold for tonic-clonic seizures. Seven patients received 0.6 Gm. of "mesantoin" daily for four days, with no signs of toxicity. The threshold for

tonic-clonic seizures was definitely increased in 5 of the patients. Four of these sustained only psychomotor seizures. In the fifth only a purely clonic seizure could be obtained.

COMMENT

The most consistent finding in the present investigation was the ability of diphenylhydantoin to abolish the tonic phase of electroshock seizures in man. Purely clonic convulsions were never observed in control patients but were typically present in patients receiving diphenylhydantoin in doses within the therapeutic range for epilepsy. One might ask whether the same action by which this drug modifies the electroshock pattern in normal man can account for the prevention of spon-

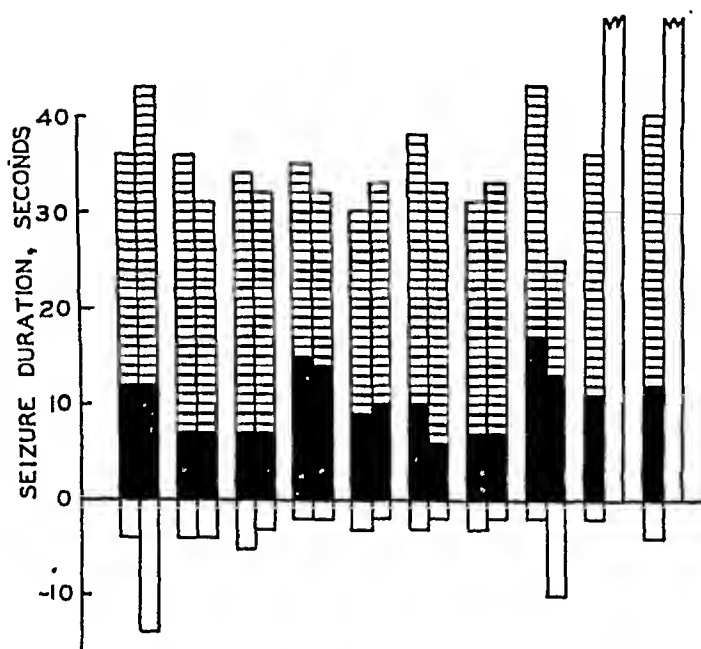


Fig. 7.—Effect of “mebaral” (*N*-methyl, 5-phenyl, 5-ethyl barbituric acid) on the pattern and duration of electroshock seizures in 10 patients. The first 7 patients (at the left of the figure) received 0.8 Gm., and the remaining 3 patients 1.2 Gm., of “mebaral” daily for three days.

taneous seizures in epileptic patients. The therapeutic mechanism would appear to be something other than an increase in seizure threshold. Previous experimental observations in animals have demonstrated the inability of diphenylhydantoin to raise the normal threshold to electroshock seizure.⁹ This does not exclude the possibility that diphenylhydantoin may act clinically by elevating abnormally lowered thresholds toward normal levels. Such an effect has been demonstrated experi-

9. Goodman, Swinyard and Toman.^{1a-c} Goodman, Toman and Swinyard.^{1e} Swinyard and Goodman.^{1f} Toman, Swinyard and Goodman.^{1j}

mentally in rats whose threshold for electroshock seizures was decreased by depletion of extracellular electrolyte.¹⁰ However, diphenylhydantoin is less effective in this respect than other anticonvulsants, including phenobarbital and trimethadione.

Another possible mechanism deserves mention. We have previously pointed out that electroencephalographic records of seizures in animals are considerably modified by diphenylhydantoin. In particular, the frequency of spike discharges characteristic of maximal seizures is much reduced.¹¹ "Spike" activity is commonly observed as a focal disturbance in the interseizure electroencephalographic records of patients with a history of convulsions. It is conceivable that diphenyl-

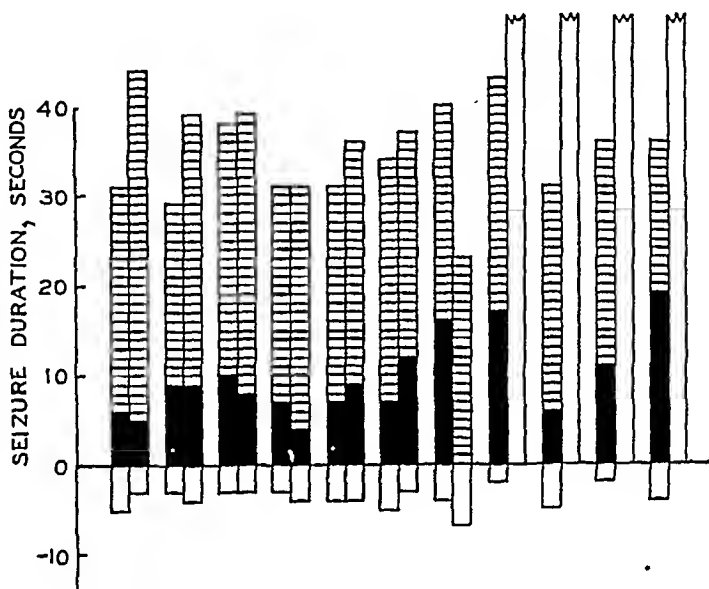


Fig. 8.—Effect of "mesantoin" (*N*-methyl, 5-phenyl, 5-ethyl hydantoin) on the pattern and duration of electroshock seizures in 11 patients. The first 3 patients (starting at the left of the figure) received 0.4 Gm. of "mesantoin" daily for four days; the remaining 8 patients, 0.6 Gm. daily for four days.

hydantoin may act by preventing these isolated "spike" discharges from attaining high frequency and spreading to normal cerebral tissue.

No systematic study of the effect of drugs on the threshold for minimal psychomotor seizures in human subjects was attempted in this investigation. Such a study entails the use of intensities of current which fail to evoke convulsions. The psychic trauma of subconvulsive stimulation is usually believed to detract from the salutary effects of electroshock therapy. Although some anticonvulsant drugs, including trimethadione and phenobarbital, have been shown to produce

10. Swinyard, Toman and Goodman.^{15, 16}

a moderate increase in threshold for electroshock convulsions in experimental animals, diphenylhydantoin fails to do so. On the basis of observations on animals, we have previously suggested that the clinical value of an anticonvulsant drug need not be correlated with ability to increase the normal threshold for electroshock seizures.¹¹

The doses of drugs used in this investigation were within or above the usual range for the therapy of clinical seizures. Inasmuch as adequate doses of trimethadione failed to alter the pattern or the threshold of seizures, it can only be concluded that the specificity of action of this drug on petit mal is dependent on some property other than those investigated. Among the other properties of trimethadione which have been investigated in animals, the preeminent one is its ability to protect against drug-induced seizures and slow wave electroencephalographic dysrhythmias. The relation between these actions of trimethadione and its specificity of action in petit mal has been discussed in full elsewhere.¹²

The limited data in this series do not permit an accurate comparison of anticonvulsant potency. With more patients and a wider range of medication, it would be possible to determine the dosage level (T) producing toxic signs in 50 per cent of patients, and the dose (P) preventing the appearance of a tonic phase in 50 per cent of patients. A protective index (T/P) could then be calculated, as in previous observations on animals.¹³ The present data suggest that the index for diphenylhydantoin would be considerably greater than 1.0 and that "mesantoin" would also rank high. Phenobarbital, sodium bromide and "mebaral" would probably rank together, with an index close to unity. The results with trimethadione are inconclusive, since neither toxic nor effective levels were reached, although the doses employed were more than adequate for the control of clinical petit mal.

In conclusion, the present data seem sufficiently encouraging to justify the use of human subjects for a quantitative comparison of the action of anticonvulsant drugs.

SUMMARY

Data are presented on the ability of anticonvulsant agents to prevent tonic-clonic seizures in nonepileptic patients undergoing electroshock therapy.

Diphenylhydantoin in nontoxic doses consistently abolishes the tonic phase of electroshock seizures. "Mesantoin" (*N*-methyl, 5-phenyl, 5-ethyl hydantoin) also ranks high in ability to modify the pattern of

11. Goodman, Swinyard and Toman.^{1b} Goodman, Toman and Swinyard.^{1c} Swinyard and Goodman.^{1f} Swinyard, Toman and Goodman.^{1h} Toman, Swinyard and Goodman.^{1j}

convulsions. Phenobarbital, sodium bromide and "mebaral" (*N*-methyl, 5-phenyl, 5-ethyl barbituric acid) are effective, but only in doses which occasionally produce undesirable side effects. "Tridione" (trimethadione) is ineffective in modifying the electroshock seizure pattern when given in doses more than adequate to control clinical petit mal epilepsy.

It is suggested that the modification of the electroshock seizure pattern in man offers a convenient method for the evaluation of potentially useful anticonvulsant drugs.

University of Utah School of Medicine.

INFLUENCE OF ANXIETY ON ATTENTION, LEARNING, RETENTION AND THINKING

OSKAR DIETHELM, M.D.

AND

MARSHALL R. JONES, Ph.D.

NEW YORK

IN THE investigation of the influence of emotions on psychologic functions by one of us (O. D.), it became apparent that the technical characteristics of many of the tests used more or less commonly by psychiatrists were not known. Consequently, a preliminary study was made to determine the reliability and other characteristics of several of these tests. These results are reported in the first part of this paper, whereas in the second part the results of the influence of anxiety on some of the tests are given. In the third part, the application of these results to the customary psychiatric examination is reviewed.

TECHNICAL CHARACTERISTICS OF SOME CLINICALLY USED TESTS

In order to be able to investigate the psychopathologic influences of anxiety on intellectual functions, tests were chosen for the study of attention, learning, retention, memory and thinking. Tests were selected which have been used in psychopathologic research work and in clinical psychiatry. Test scores were obtained in some cases from normal women college students and in some cases from psychiatric patients of the type on whom it was desired to use the tests later for further research.

Attention.—Although the concept of attention is greatly disputed in present day psychology, attention and its disorders have maintained an important place in psychopathology and clinical psychiatry. In our investigations, we were forced to consider the Wundtian distinction between active and passive attention because of the claim of leading psychopathologists that various mental disorders affect these two types of attention independently.¹ These authors distinguish between an

From the New York Hospital and the Department of Psychiatry, Cornell University Medical College.

Miss D. Kearton, Miss M. Jackson and Miss M. Guy assisted in collecting part of the data on this experiment.

1. Bleuler, E.: *Lehrbuch der Psychiatrie*, ed. 7, Berlin, Julius Springer, 1943.

13 14 15
 poses./ It had been built fifty years/ before I was born./ The old inhabitants
 16 17 18
 said/ that when it was built/ the barn was the best known/ in the country/ and,
 19 20 21
 although other barns/ of greater size/ and of more ornate appearance/ had been
 22 23 24
 erected/ in more recent years,/ they still continued to talk of it/ as one of the
 25 26 27
 most wonderful buildings/ in existence./ The building had been used/ for other
 28 29 30 31 32
 purposes/ than that of a barn./ It contained/ a wonderful collection/ of tools/
 33 34 35 36
 of all kinds/ and several neat workshops/ that were well stocked/ with woods/
 37 38 39
 of all kinds./ Adjoining it was a barnyard/ laid out at a later date/ but with
 40 41 42 43 44
 small houses/ for the chickens/ and ducks/ which were miniatures/ of the large
 barn building./

Learning and Retention.—Learning and retention were studied by means of two stylus mazes. Each maze consisted of a single correct path, with five blind alleys. Maze 1 had 24 turns; maze 2 had 29. The subjects were trained to the criterion of three successive errorless trials, or for a period of seventy-five minutes if they had not reached the criterion by that time. They were retrained twenty-four hours later on the same maze to the same criterion. Errors were scored in the usual manner, and the corrected odd-even reliability coefficient for error scores for maze 1, in both the original and the relearning test, was 0.86; and for maze 2 they were 0.90 and 0.94.

In order to determine whether the two mazes were of equal difficulty, and whether if the experience of learning one maze would carry over for as long as six weeks in such a way as to facilitate the learning of the second maze, maze 2 was given to 30 psychoneurotic and depressed patients six weeks after maze 1 had been learned successfully, while to another group of 30 psychoneurotic and depressed patients maze 2 was given first, followed six weeks later by maze 1. It was found that the two mazes are of practically equal difficulty and that there was no appreciable carry-over of maze learning ability from one test to the other, as measured by errors, number of trials or speed.

Immediate Memory.—The fixation of new impressions was first determined by using two brief paragraphs from the Thorndike-McCall Reading Scale (stories of Dick and of Nell). Both stories were far too easy and had too few units. The odd-even reliability coefficients were not greater than their probable errors. This test was therefore abandoned.

The "Cowboy Story," which is used in psychiatric examination (from the original 1916 Stanford-Binet scale), gave better results. The story

was divided into 27 logical units. This test was given to 31 patients. The corrected odd-even reliability coefficient for the number of units retained was 0.94. The "Cowboy Story" can be used as a reliable means of discriminating between patients on the basis of immediate memory. The story, with the units used, follows.

1 2 3 4 5

A cowboy/ from Arizona/ went to San Francisco/ with his dog,/ which he

6 7 8 9

left/ at a friend's/ while he purchased/ a new suit of clothes./ Dressed finely,/ he

10 11 12 13 14

went back/ to the dog,/ whistled to him,/ called him by name/ and patted him./

15 16 17

But the dog would have nothing to do with him,/ in his new hat/ and coat,/ but

18 19 20 21

gave a mournful/ howl./ Coaxing was of no effect/; so the cowboy went away/

22 23 24 25

and donned his old garments,/ whereon the dog/ immediately/ showed his wild

26 27

joy/ on seeing his master/ as he thought he ought to be./

Thinking.—Two tests were selected which have been used in psychiatric practice in the study of schizophrenic and senile thinking disorders. The Kohs Block Test may be used to investigate the speed of forming a pattern, involving the ability to discriminate different forms and their spatial relations. The Hausmann absurdity test³ has been recommended for determination of schizophrenic thinking disorders.

1. Kohs Block Test: In our administration of this test, only the time score was used. For 66 patients, the corrected odd-even reliability coefficient was 0.96.

2. Hausmann's Test for Appreciation of Absurdities: This test was found to have practically zero reliability with 48 students. In a study on 24 psychiatric patients of above average intelligence and of ages varying from 18 to 45, the corrected odd-even reliability coefficient was found to be 0.57. In its present form the test is obviously valueless, but, as the low reliability is most likely related to the small number of units in the test, the test might be made useful by lengthening it.

INFLUENCE OF ANXIETY

The patients studied (all of whom were under treatment in the inpatient department of the Payne Whitney Clinic) were of superior intelligence. Their ages varied from 20 to 49. In all the patients anxiety was present in pathologic intensity, either as one of the most prominent symptoms, in the depressed patients, or as the outstanding symptom, in the psychoneurotic patients. The intensity of the anxiety

3. Muncie, W.: *Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior*, St. Louis, C. V. Mosby Company, 1939.

was estimated by subjective descriptions of anxiety and its physical accompaniments and by the observations on increases in pulse rate, sleep disorders, variations in food intake, increases in the fasting blood sugar and the leukocyte count⁴ and other psychopathologic phenomena attributable to anxiety. In 20 patients, adrenergic-cholinergic substances in the blood were determined in the evaluation of anxiety.⁵ Some of the psychologic tests which were discussed in the preceding pages were given when the patient experienced intense anxiety and were repeated when the anxiety had subsided. The minimal interval between test and retest was six weeks, but the period was usually two to three months and occasionally longer. With a considerable number of patients, a retest was not possible because they left the clinic before the time for retest had arrived, or at a time when testing was not possible for other reasons. A small group of 6 patients was studied when anxiety was greater at the time of the retest.

TABLE 1.—*Scores for Data on the Forward Digit Span Test*

	Mean		Critical Ratio * (D/s.e.diff.)
	First Test (Intense Anxiety)	Second Test (Less Anxiety)	
Longest span before error.....	6.0	6.9	2.6
Longest span before two consecutive errors.....	7.0	7.4	1.5
Longest span regardless of errors.....	7.1	7.6	1.0

* The critical ratio is the difference of the means divided by the standard error of the difference.

Attention.—(a) Directed Attention, Studied by the Digit Span: The forward digit span was given to a group of 35 patients who had intense anxiety at the time of the first test and whose anxiety had decreased at the time of the second test. When the results were scored for the number of errors before the last correct series, the mean score for forward repetition was 0.89 error and on the retest the mean score was 0.74 error. The critical ratio of the difference between these means does not approach statistical significance; so it must be said that a change in the clinical picture of the patient was not accompanied with a change in the results of the test when scored this way.

Table 1 gives the results of this test when it is scored in the three more conventional ways and when results obtained under the influence of different degrees of anxiety are compared. The critical ratio of the

4. Milhorat, A. T.; Small, S. M., and Diethelm, O.: Leukocytosis During Various Emotional States, *Arch. Neurol. & Psychiat.* **47**:779-792 (May) 1942.

5. Diethelm, O.; Doty, E. J., and Milhorat, A. T.: Emotions and Adrenergic and Cholinergic Changes in the Blood, *Arch. Neurol. & Psychiat.* **54**:110-115 (Aug.) 1945.

difference between the means on test and retest, when scored in terms of the longest span repeated before any error is made, approaches statistical significance, and it is therefore possible that a decrease in anxiety has operated to improve this score.

The reversed digit span was scored in the same ways. The mean number of errors before the longest possible span on the first test was 0.94 and that on the retest 0.83. This difference, of course, is not statistically significant.

Table 2 gives the data for the reversed digits scored in the more conventional manner.

These results are at odds with clinical experience, and the absence of a significant increase of the second score over the first is especially hard to explain when practice effect should operate in this direction also.

These data suggest that anxiety decreases active attention as measured by the longest span of attention before the error is made. No

TABLE 2.—*Scores for Data on the Reversed Digits Span Test*

	Mean		Critical Ratio (D/s.e.diff.)
	First Test (Intense Anxiety)	Second Test (Less Anxiety)	
Longest span before error.....	5.0	5.6	1.9
Longest span before two consecutive errors.....	6.1	6.5	1.2
Longest span regardless of errors.....	6.3	6.6	1.0

statistically significant changes were found when the digit span was scored by the longest span before two consecutive errors or by the longest span regardless of errors. The reversed digit span was not affected significantly by anxiety.

(b) *Passive Attention, Studied by the "Barn Story"*: Forty-seven students recalled a mean number of 9.1 units in this story immediately after it was read. Fifty-four patients who revealed definite signs of anxiety at the time of the test obtained a mean score of 6.5 units. The critical ratio of the difference between these means is 2.24, thus indicating that the probability that this represents a real difference is better than 99 in 100. The students' scores showed greater variability, as indicated by a standard deviation of 6.2 and a range of 0 to 26, whereas the patients' distribution had a standard deviation of 5.5 and a range of 0 to 16. The greater variability in the distribution of students' scores is in part at least attributable to the concentration of patients' scores at the lower limit of the range. These results must be interpreted cautiously, since the two groups were unmatched on several variables which could conceivably contribute to the difference between the mean

scores. However, there is some indication that anxiety may have been a factor in reducing scores in view of the fact that 17 patients who showed pronounced anxiety all scored between 0 and 5.

Learning (studied by means of the maze test).—With 57 patients it was possible to study learning in a repeat test when anxiety had subsided.

Since a control test showed no reliable decrease in mean scores on a second maze test over a comparable period, these results indicate that learning is reliably slower in the presence of anxiety. Notable changes were observed in all three fields—error, trials and time—but not always concurrently. The extreme variation for 1 patient was from 154 errors, 28 trials and 1,665 seconds with intense anxiety to 66 errors, 19 trials and 742 seconds in the retest when anxiety was mild. The most extreme variation in errors was from 180 to 47; in trials, from 32 to 2, and in time, from 1,943 to 161 seconds. On the whole, the most pronounced improvement in all three factors

TABLE 3.—Scores for Data on Learning in Retest

	Mean		Critical Ratio (D/s.e.diff.)
	First Test (Intense Anxiety)	Second Test (Less Anxiety)	
Errors.....	109.7	75.1	2.9
Trials.....	20.5	14.2	3.1
Time, sec.	1,541.9	960.2	3.9

was observed in patients who experienced intense anxiety during the first test and little anxiety during the repeat test. It is impossible to state whether any one of these three factors was affected more frequently or more markedly than the others. With 3 patients, anxiety was greater at the time of the retest than on the first test. This anxiety subsided the same day. With these 3 patients learning was affected adversely. For 2 of the patients the time for learning the test was increased; the third patient, on the other hand, showed a significant increase in trials, whereas the errors and time had decreased significantly. In 1 patient, an insecure person with high standards, anxiety became stirred up during the test when he made several errors in the beginning, and the total results were considerably less good than in the first test, although his intense anxiety had subsided greatly during the course of his illness.

Eleven patients failed to learn the maze. For 7 of these patients the learning scores were above the mean when their intense anxiety had subsided. For the remaining 4 patients learning scores were below the mean at a time when they still experienced considerable anxiety.

The findings on the maze test suggest that learning is slower in the presence of anxiety.

Retention (studied by means of the maze test).—Retention ability was tested by repeating the maze twenty-four hours after it was learned on each of two occasions, once when the patient revealed much anxiety and later, on the second maze, when anxiety was reduced.

Fifty-seven patients learned the maze at the first attempt. Table 4 gives the mean number of errors, trials and seconds required to relearn the maze twenty-four hours after the original learning.

When anxiety was greater, the number of trials was significantly greater. The extremes observed were 21 trials, under intense anxiety in the first test, and 6 trials, without anxiety in the retest four months later. A difference of 10 to 12 trials was frequent under the influence of anxiety. In 3 patients anxiety had increased at the time of the retest. This anxiety was only transient, lasting a few hours on the day of the test for retention, but was sufficient to affect retention unfavorably. For

TABLE 4.—Data on Relearning the Maze Test

	Mean		Critical Ratio (D/s.e.diff.)
	Relearning with Intense Anxiety	Relearning with Less Anxiety	
Errors.....	16.9	8.8	1.9
Trials.....	6.0	3.0	3.2
Time, sec.	289.9	158.8	2.4

2 of these patients the errors and the time increased markedly, whereas the number of trials increased less. For a third patient errors increased markedly, whereas the number of trials and the time decreased.

The findings suggest that retention ability is affected unfavorably by anxiety.

Thinking (studied by means of the Kohs Block Test).—To 64 patients, the Kohs Block Test was administered under conditions of extreme anxiety in the first test and less or no anxiety in the retest. The mean score for the first test was 90.2, and that for the retest, 110.6,⁶ giving a critical ratio of the difference of 4.2, representing probably a real improvement. (Experience in intelligence test batteries shows that the Kohs Block Test can be repeated after a short interval of time without appreciable practice effect.) The extremes observed were a score of 41, in the first test, and of 116, in the retest. For most patients the difference was from 20 to 40 points. For 18 patients the score was low, i. e., 8 to 73 in the first test. For 10 of these 18 patients there was an increase of 20 to 40 points in the retest without the influence

6. Higher scores are better in this test.

of anxiety; for 2 patients, an increase of 56 and 67 points, respectively, and for 6 patients, less than 20 points. For 8 patients, the first score was over 120 under the influence of anxiety, with an increase of only a few points without anxiety, i. e., a statistically insignificant change. For 6 patients the first score was over 120, and there was a notable increase (11 to 14 points) with lessened anxiety. For the majority of the patients (34), the test score under the influence of anxiety was between 75 and 120 and the increase under the influence of little or no anxiety was 12 to 38 points, 2 patients showing an increase of only 4 and 6 points, respectively, and 1 patient an increase of 45 points.

It seems that anxiety decreases the score significantly for most patients, but that there is a small group which is influenced little.

EVALUATION OF ANXIETY IN PSYCHIATRIC EXAMINATION

The standard psychiatric examination which has been developed in American psychiatry during the last forty years represents an attempt at objective determination of psychopathologic phenomena. Some of the tests discussed in the preceding pages are used in psychiatric examination, but what is to be studied through them is frequently not recognized by the physician. A brief review of the meaning of a psychiatric examination therefore seems indicated. It is also hoped that a clinically acceptable standardization of the present type of psychiatric examination will evolve.

Under "appearance and behavior" are noted findings which are indicative of the type of rapport, the patient's spontaneous and reactive behavior, motility disorders, dissociation and personality disorganization. The "characteristics of talk" reveal disorders of thinking and of symbolization, a tendency to substitution and dissociation. The observations noted under "emotional state and reactions" permit the physician to recognize various emotional disorders and the psychopathologic significance of any emotion present. Under "special preoccupations and experiences," or "topical material" or "content," as it is also called, dynamic factors can be seen, either directly or in the form of projections. It can be judged whether these findings are linked to intense emotional reactions and, if so, whether the emotions are largely dependent on the preoccupations or, on the contrary, cause them. "Orientation" is indicative of the clearness of consciousness and grasp, their disturbance being primarily due to toxic and organic factors and less frequently to psychodynamic factors or intense emotions. Under "Memory," recall of experiences in the remote and recent past and of immediate impressions are tested, and disorders in this field are indicative of cortical disturbance. These disorders may be of permanent nature, as in the "organic" psychoses, or transient, as in the various types of delirious disorders and

in severe disorders of thinking of the affective and schizophrenic types. Memory disorders may occur to a less extent under various emotional influences. Tests of recall of immediate impressions (repetition of three nonrelated words and recall after three minutes) and of general grasp and recall of a story which the patient has read aloud ("Cowboy Story") demonstrate readily the presence of confabulation. (Contrary to the general assumption, there is no test in the psychiatric examination to evaluate retention directly.) The "span of attention" is investigated by immediate repetition of digits, starting with three digits and increasing until the first failure. An additional test may be given in which the patient is requested to repeat the digits in reverse order. The simple "concentration test" of serial subtraction of 7 from 100 is valuable clinically. Intense emotions affect attention and concentration and, to a less extent, general grasp and recall. "General intellectual evaluation" (i. e., rough evaluation of general information, calculation, reasoning and judgment) is studied for the recognition of disorders of intellectual functions which may be due primarily to cortical damage, acquired prenatally, early or late in life, or to sweeping affective disorders, special preoccupations and thinking disorders. Failure in calculation may be due to general intellectual defects, thinking and attention disorders and to fatigue. Judgment is affected in any of the aforementioned disorders and under catathymic influences. "Insight" indicates the patient's awareness of his being ill, of the character of his illness and of the special dynamic factors involved.

This study was undertaken especially to gain an understanding of the influence of anxiety on psychologic functions. It demonstrates that anxiety affects attention, concentration, learning, retention and, to some extent, thinking. In any psychiatric examination one should always evaluate the influence of anxiety. It may be possible to gage the intensity of this emotion from the findings in the psychiatric examination. Unusual findings in the realm of the functions indicated should prompt the examiner to look for emotional factors. A psychiatric examination is therefore valuable in any evaluation of emotions in whatever psychologic or psychopathologic setting they occur, i. e., whether the disturbance is considered psychoneurotic, psychotic or psychosomatic. (It should be stressed that it is undesirable to use the term "psychotic," which does not connote a contrast to "psychoneurotic" and is a generalization which is as inaccurate as the older term "insane.")

It is to be expected that emotions other than anxiety affect various psychologic functions. Anxiety was selected because combined physiologic-psychopathologic studies have demonstrated the influence of this emotion on physiologic functions. Our findings, therefore, permit an objective evaluation of anxiety. Similar evaluation is at present possible with regard to tension, fear and resentment, whereas the emotions of

depression and mild elation do not seem to influence the physiologic functions studied. In the field of psychopathology, the depressive emotions have been credited with far reaching effects. It is most questionable whether depressive emotions cause severe thinking disorders of the type of confusion and memory and retention difficulties. It is more likely that anxiety, which seems to be present in every pathologic depressive reaction, causes these disorders. The effects of the depressive emotions can be established only when it becomes possible to study them without the presence of anxiety. A similar difficulty arises in the study of psychopathologic elation. In a study on the measurement of hyper-associative activity during elation,⁷ it was possible to demonstrate increased speed of thinking under the influence of elation. Some of the patients in this study did not give an indication of the presence of anxiety. No patient who suffered from intense anxiety without elation showed increased speed of thinking. The conclusion, therefore, seems warranted that elation was the essential factor. On the other hand, it is uncertain whether anxiety is not a contributory, or even a necessary, factor in pathologic elation.

A psychiatric examination presents a group of experiments which cannot be evaluated independently of each other. In every experiment the attitude of the subject to the situation is of great importance. In the study of maze learning, anxiety with respect to the test interfered greatly with learning, and the anxiety resulting from difficulty in learning affected retention. This anxiety could affect other tests which might be given immediately after the maze test. The same reaction may occur during a psychiatric examination. Anxiety which had not been very active before the examination may become intense with the questioning, and may increase or decrease during the further progress of the test.

SUMMARY

A group of tests were selected for the study of active and passive attention, learning, retention, immediate memory and thinking. The reliability was established in all tests which were used in this study.

Anxiety appears to decrease active attention, as measured by the longest span of digits before an error is made. Passive attention, as studied by the recall of the number of units of the "Barn Story," was affected adversely by intense anxiety. This effect was less clear when anxiety was not intense. Learning on the maze test was reliably slower in the presence of anxiety. Retention ability, tested by repetition of the maze test twenty-four hours after it was learned, was affected unfavorably by anxiety. Thinking was studied by means of the Kohs Block

7. Welch, L.; Diethelm, O., and Long, L.: Measurement of Hyper-Associative Activity During Elation, *J. Psychol.* **21**:113-126 (Jan.) 1946.

Test. It seems that anxiety decreases the score significantly with most patients, but there is a small group which is influenced little. The influence of anxiety in the different experiments was not uniform. It may happen that one or the other of the aforementioned functions is affected little, whereas all or the majority of the remaining functions are affected to a pronounced degree.

The possible influence of anxiety on the various functions which are tested in the current type of psychiatric examination has to be considered more seriously than has been done heretofore. It may be possible to gage the intensity of anxiety from the findings. It is necessary, however, that the technic of the examination be refined by a careful scoring of the "Cowboy Story" test and by the inclusion of additional tests which have been found useful and reliable in psychologic study.

New York Hospital.

EFFECT OF QUINACRINE (ATABRINE) ON THE CENTRAL NERVOUS SYSTEM

Clinical and Electroencephalographic Studies

GEORGE L. ENGEL, M.D.

AND

JOHN ROMANO, M.D.

ROCHESTER, N. Y.

AND

EUGENE B. FERRIS, M.D.

CINCINNATI

THE INTRODUCTION of quinacrine hydrochloride (atabrine dihydrochloride) as an antimalarial agent has brought with it the usual problem of untoward reactions with which physicians must become familiar. Important among the toxic effects encountered have been psychotic reactions. The appearance of such reactions during the widespread use of this drug in the armed forces, as well as indications that some of the related antimalarial compounds being studied might also have an effect on the central nervous system, led to a request by the Board for the Coordination of Malarial Studies that we investigate this action of the drug in human subjects. The results of this study were transmitted to the Board in the summer of 1944.

Gaskill and Fitz-Hugh¹ recently reported on the incidence of such "toxic psychoses" among patients with malaria who had been treated with quinacrine. In seven months' experience in an army hospital in a highly endemic area, to which 7,604 patients with malaria were admitted, these authors encountered 35 persons in whom a "toxic psychosis" developed, an incidence of 0.4 per cent. The time of onset of the reaction varied from the third day of administration of quinacrine to twelve days after the last dose of the drug, the most common date of onset being the sixth day after completion of the therapy, the usual total dose of the drug being 2.1 Gm. Since the onset of the psychosis

From the Departments of Psychiatry and Internal Medicine, University of Cincinnati College of Medicine.

The work described in this paper was carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Cincinnati.

1. Gaskill, H. S., and Fitz-Hugh, T., Jr.: Toxic Psychoses Following Atabrine, Bull. U. S. Army M. Dept., 1945, no. 86, p. 63.

was often insidious, the authors stated the opinion that more careful observation might have disclosed an earlier date of onset. They described two types of responses: The first was characterized by sudden increase in motor and psychomotor activity, frequently accompanied with auditory and visual hallucinations, delusions and ideas of references, and an affect of euphoria and expansiveness. The second type began more insidiously with gradual clouding of the sensorium, disorientation, loss of memory for recent events and diminution of activity in both the intellectual and the motor sphere, with a predominant affect of bewilderment and fearfulness. The authors pointed out that the symptoms were apparently colored in part by the prepsychotic personality of the individual patient.

This excellent clinical report leaves unanswered several important questions. While the late onset of the reactions is strong presumptive evidence that they were induced by the quinacrine, the role of the pre-existing malarial infection together with the fatigue, undernutrition, dehydration, previous combat experience and other factors that might be expected among this group of patients is difficult to evaluate. The authors attempted to test this point by administering a second course of quinacrine to 16 of the patients who had recovered from a psychosis. Two of the patients received the drug because of a recurrence of malaria. Each patient received 0.2 Gm. of quinacrine hydrochloride every six hours for five doses, followed by 0.1 Gm. three times daily for six days, making a total of 2.8 Gm. Only 1 subject exhibited any untoward reaction. This patient became mildly excited on the last day the drug was administered, recovering completely in forty-eight hours. From these results the authors suggested the following alternative hypotheses:

. . . There is no specific causal relationship between atabrine and these psychoses; these toxic psychoses represent an unusual sensitivity reaction to atabrine in which at least temporary desensitization is produced by the attack; or this psychosis is a complex-conditioned sensitivity in which atabrine is one of several factors which must coincide in a given individual in order to produce this syndrome.

The influence of some of these complicating factors can be eliminated by studying the effects of quinacrine on normal healthy adults. Previous studies of delirium, both as experienced spontaneously in the course of various diseases² and as induced experimentally by anoxia,³ hypo-

2. (a) Romano, J., and Engel, G. L.: Delirium: I. Electroencephalographic Data, *Arch. Neurol. & Psychiat.* **51**:356 (April) 1944. (b) Engel, G. L., and Romano, J.: Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedures, *ibid.* **51**:378 (April) 1944.

3. Engel, G. L.; Webb, J. P., and Ferris, E. B.: Quantitative Electroencephalographic Studies of Anoxia in Humans: Comparison with Acute Alcoholic Intoxication and Hypoglycemia, *J. Clin. Investigation* **24**:691, 1945.

glycemia³ and the administration of alcohol⁴ and other toxic materials,⁵ have yielded a technic ideally suited to this purpose. In these studies it was found that the electroencephalogram provided a sensitive indicator of changes in the physiologic status of the cortex under the circumstances previously cited. With the use of a quantitative method of analysis of frequency distribution in the electroencephalogram,⁶ it proved possible to correlate the level of consciousness with changes in frequency distribution. In general, reduction in the level of awareness was found to be associated with a shift toward slower frequency ranges; in the more extreme cases this was accompanied with a notable disruption of synchrony, as evidenced by the appearance of low voltage fast activity. Studies of the behavior of the patients and of the experimental subjects revealed that the basic psychologic disturbance in delirium is a reduction and an increased fluctuation in the level of awareness, and that the intellectual, emotional and motor behavior of these persons may best be understood in terms of a release of less well integrated or more primitive behavior resulting from reduction of higher cortical control.

It seemed likely from these earlier studies that if quinacrine, in reasonable dosage, exerted any influence on the cerebral cortex of normal human subjects, it should be possible with this electroencephalographic technic to detect such an effect even before clinical changes were apparent. Pick and Hunter⁷ reported changes in the electroencephalograms of cats under pentobarbital anesthesia and of pithed frogs during the administration of quinacrine. These observers noted the disappearance of fast activity and the development of slow waves of low amplitude. The dosage and the blood levels of quinacrine, however, were very high.

DESIGN OF EXPERIMENT

Five normal men, aged 26, 29, 30, 35 and 39, received quinacrine hydrochloride. A sixth subject, a man aged 30, served as a control. He received no quinacrine and was studied simultaneously with the experimental subjects. During a control

4. (a) Engel, G. L., and Rosenbaum, M.: Delirium: III. The Electroencephalographic Changes Associated with Acute Alcoholic Intoxication, *Arch. Neurol. & Psychiat.* **53**:44 (Jan.) 1945. (b) Engel, Webb and Ferris.³

5. Engel, G. L.; Romano, J., and Goldman, L.: Delirium: IV. Quantitative Electroencephalographic Study of a Case of Acute Arsenical Encephalopathy, *Arch. Neurol. & Psychiat.* **56**:659 (Dec.) 1947.

6. Engel, G. L.; Romano, J.; Ferris, E. B.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram: Observations on the Effects of Physiological Variations in Dextrose, Oxygen, Posture and Acid-Base Balance on Normal Electroencephalogram, *Arch. Neurol. & Psychiat.* **51**:134 (Feb.) 1944.

7. Pick, E. P., and Hunter, J.: The Action of Atabrine on the Electro-cortico Potentials, *J. Pharmacol. & Exper. Therap.* **80**:354, 1944.

period of five to six days, all the subjects had electroencephalographic recordings twice daily, morning and afternoon, with simultaneous determinations of the blood sugar. During this period physical and neurologic examinations were carried out, and subjective and objective data on behavior were noted daily. Each of the 5 experimental subjects was then given 0.2 Gm. of quinacrine hydrochloride every four hours for the first twenty-four hours (total, 1.2 Gm.) and a total of 0.2 to 1.2 Gm. daily (in divided doses every four to eight hours) until the plasma level of the drug exceeded 100 micrograms per liter or until severity of symptoms necessitated discontinuance of administration of the drug or reduction of the dose. The daily doses for each subject are indicated in charts 1 to 5. It will be noted that plasma levels of 100 micrograms per liter or higher were obtained within six to ten days in 4 subjects and that the fifth subject discontinued taking the drug on the third day (plasma level of quinacrine, 75 micrograms per liter) because of the severe symptoms. No subject received quinacrine longer than ten days. During the period of administration of the drug simultaneous electroencephalographic recordings and determinations of the blood sugar, the plasma level of quinacrine and the rectal temperature (starting on the sixth day) were made twice daily, and subjective and objective data on behavior were noted. Similar observations were carried out until the twentieth day after administration of the drug had been initiated (ten to seventeen days after it had been discontinued). During the last six days observations were made only once daily. After a lapse of fifty-three days, to permit excretion of the drug, the subjects were observed twice daily for a third period, of four days. The control subject was studied simultaneously.

A three channel electroencephalograph, constructed by Mr. Albert Grass, was utilized in these experiments. Bipolar fronto-occipital tracings were obtained. A quantitative method of frequency analysis, described in detail elsewhere,⁸ was employed. Briefly, this involved counting the number of waves per second interval for a two hundred second strip and determining the percentile distribution of each wave frequency, which could then be expressed as a spectrum. From this, the mean frequency could be calculated by taking the arithmetical mean of the frequencies represented. The mean frequency yielded an adequate index of the shifts in frequency under the conditions of these experiments. For brevity's sake, the more extensive and space-consuming spectrums are omitted here except for a single illustrative sample (chart 6). All subjects had control electroencephalograms with over 95 per cent well developed alpha activity. Since the accuracy of the method is far greater in such circumstances, and since it is difficult or impossible to derive a mean frequency if the record contains much uncountable low voltage fast activity, subjects with good alpha rhythm were intentionally selected. Three of the subjects had had many previous electroencephalograms during the past two years, and the mean frequencies for these subjects had shown little fluctuation over that period. The range of daily variation in mean frequencies (for each subject) in the control period is illustrated in charts 1 to 5. The reliability and validity of this method are discussed in more detail in the references previously cited.⁹

The plasma levels of quinacrine were determined by the Masen method¹⁰ under the direction of Dr. Leon Schmidt, Christ Hospital, Cincinnati.

8. Engel, Webb and Ferris.³ Engel and others.⁶

9. Engel and Romano.² Engel, Webb and Ferris.³ Engel and Rosenbaum.^{4a} Engel, Romano and Goldman.⁵ Engel and others.⁶

10. Masen, J. M.: Quantitative Determination of Atabrine in Blood and Urine, *J. Biol. Chem.* **148**:529, 1943.

RESULTS

The individual data on each subject are graphically recorded (charts 1 to 5).

It will be noted from inspection of these charts that all subjects showed a sustained acceleration in frequency of the brain waves, beginning by the third or fourth day of administration of the drug and persisting for six to eight days after it had been discontinued. This increase in frequency was of pronounced degree in the records of 2 subjects, in which it was readily apparent on inspection alone (chart 6), and of moderate degree in the tracings of the remaining 3 subjects. Simultaneous measurements of the blood sugar and the rectal temperature failed to reveal any consistent trend which would account for this change in frequency of the brain waves. While no precise correlations with plasma levels of quinacrine are possible, in all instances the acceleration in frequency of brain waves appeared to be present when plasma levels of the drug exceeded 30 to 40 micrograms per liter. Since electroencephalograms and plasma levels of quinacrine were not obtained during the first two days of administration of the drug, the establishment of this effect at a lower plasma level cannot be ruled out. During the final period, after a lapse of fifty-three days, the mean frequencies were similar to those in the control period and the plasma levels of quinacrine were between 0 and 5 micrograms per liter. The electroencephalogram of the control subject showed no significant change during the course of the experiment.

Concurrently with the acceleration of the brain waves, certain psychologic symptoms appeared. All the subjects experienced some degree of motor restlessness, sleeplessness and awakening dreams, which at times were of frightening and nightmarish quality. The subjects showed psychologic acceleration and an unusual push of activity, and each subject was able to carry on more than ten to twelve hours of daily activity in the hospital and medical school. This was associated with varying amounts of tension, irritability and anxiety. In 1 subject (subject 1) this reached on the ninth day the magnitude of an acute panic reaction, with considerable flight of ideas and anxiety, and required hospitalization. This case so well characterizes the nature of the reaction that it is reported in detail.

SUBJECT 1 (chart 1).—A man aged 39, in good health, had had fourteen control electroencephalograms taken during the preceding two years. Psychologic tests of awareness had also been administered repeatedly in the course of other studies during this period. During the five days preceding the administration of quinacrine, records were taken twice daily, the mean frequency ranging from 9.07 to 9.20 per second. In the total of 24 control records during two years the highest mean frequency was 9.22 per second.

On completion of the control period, 0.2 Gm. of quinacrine hydrochloride was taken every four hours, a total of 1.2 Gm. in the first twenty-four hours, and 0.1 Gm. three times a day for the next two days. On the second day he noted slight epigastric distress and mild diarrhea. At the end of the third day the plasma level of quinacrine was 30 micrograms per liter and the mean electroencephalographic frequency was 9.59 per second. On the fourth and fifth days he took 0.2 Gm. of quinacrine hydrochloride three times daily. Mild gastrointestinal symptoms continued, and the development of pigmentation was noted. Sleep was fitful. The plasma level of quinacrine reached 55 micrograms per liter, and the mean electroencephalographic frequency was 10.25 per second. On the sixth day a total of 1.2 Gm. of the drug was taken, and the plasma level of the drug was 83 micrograms per

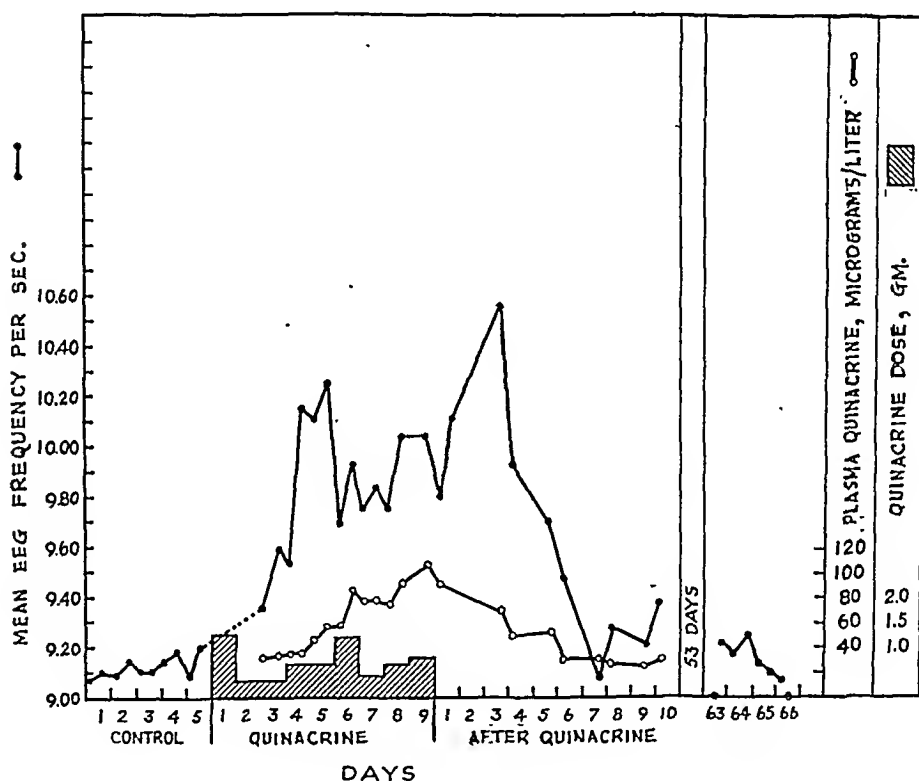


Chart 1 (subject 1).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

liter. That night he had difficulty in getting to sleep and slept fitfully. He awoke many times and had many unremembered dreams, which awakened him. The next two days (seventh and eighth) he took 0.4 and 0.6 Gm. daily, respectively, and the plasma level of the quinacrine reached 105 micrograms per liter. The mean electroencephalographic frequency fluctuated but continued to be accelerated. The symptoms continued; in addition, he noted weakness, general malaise, chilliness, sweating and aching of the extremities. The rectal temperature was 100 F. Dreams of nightmarish quality awakened him frequently. The next day he took 0.7 Gm. of the drug. That night he retired at 9 p. m. but was unable to sleep. He felt very restless and was bombarded with thoughts. He had difficulty in manipulating

the alarm clock, which rang at 11 p. m. He tried to reset it but was unable to see the alarm hand clearly. He tried to read but was too distracted by extraneous thoughts and ideas flashing into his mind. Problems seemed at first easy of solution but then became jumbled, and a montage effect was attained. He tried to write a letter but made errors and was distracted. He turned out the lights, but in the darkness the symptoms grew worse; he began to feel progressively more frightened and panicky and finally called for help. A sample of blood was drawn, yielding a plasma level of 105 micrograms of quinacrine per liter. Sodium amytal, 0.1 Gm., was administered, after which the symptoms abated somewhat and he was able to sleep. The following morning he was somewhat euphoric and joked about his experience of the previous night. However, shortly he again began to feel panicky and harassed and then depressed. Examination of the level of consciousness at this point revealed that there was no reduction of awareness; indeed, there appeared to be a heightening of awareness and an actual acceleration of mental activity. The mean electroencephalographic frequency was 10.10 per second.

The patient was hospitalized and given sodium amytal by mouth and 5 per cent dextrose in distilled water by vein. Administration of quinacrine was discontinued. The symptoms rapidly subsided and within twenty-four hours had largely disappeared. The acceleration in the mean electroencephalographic frequency continued for two days and then rapidly decreased. The plasma level of the quinacrine decreased slowly, reaching 30 micrograms per liter in ten days.

COMMENT

Initially, this reaction was interpreted as a delirium, but further scrutiny revealed that the level of consciousness was not reduced and that attention was not impaired. The subject was apparently so bombarded by stimuli that he was unable to cope with them. The apparent confusion was probably due to multiplicity of thoughts and concomitant anxiety.

Brief clinical notes on the behavior of the other subjects follow; the other data are presented graphically (charts 2 to 5).

SUBJECT 2 (chart 2).—The subject, aged 29, slept poorly and experienced a tired feeling in the legs. On the fifth day he had severe insomnia, which was unusual for him, as well as nausea, slight diarrhea, abdominal cramps, aching extremities, night sweats, chilliness, a rectal temperature of 101 to 103 F. and lassitude with restlessness. In spite of malaise and other symptoms, the subject noted a considerable push of activity and worked late at night. The maximum plasma level of the quinacrine was 102 micrograms per liter. Acceleration of the electroencephalographic frequency was striking (charts 2 and 6). The drug was discontinued on the seventh day, after which symptoms rapidly subsided.

SUBJECT 3 (chart 3).—The subject, aged 26, on the third day of administration of the drug began to note restlessness, fitful sleep and frequent awakening from bad dreams. There were mild abdominal cramps from time to time. Insomnia and anxiety dreams increased, and he had two attacks of migraine, with scintillating scotomas. On the ninth day he felt "almost euphoric" but was easily fatigued. He felt a tremendous pressure of activity and emotional lability. The drug was discontinued on the tenth day, and symptoms rapidly subsided. The maximum

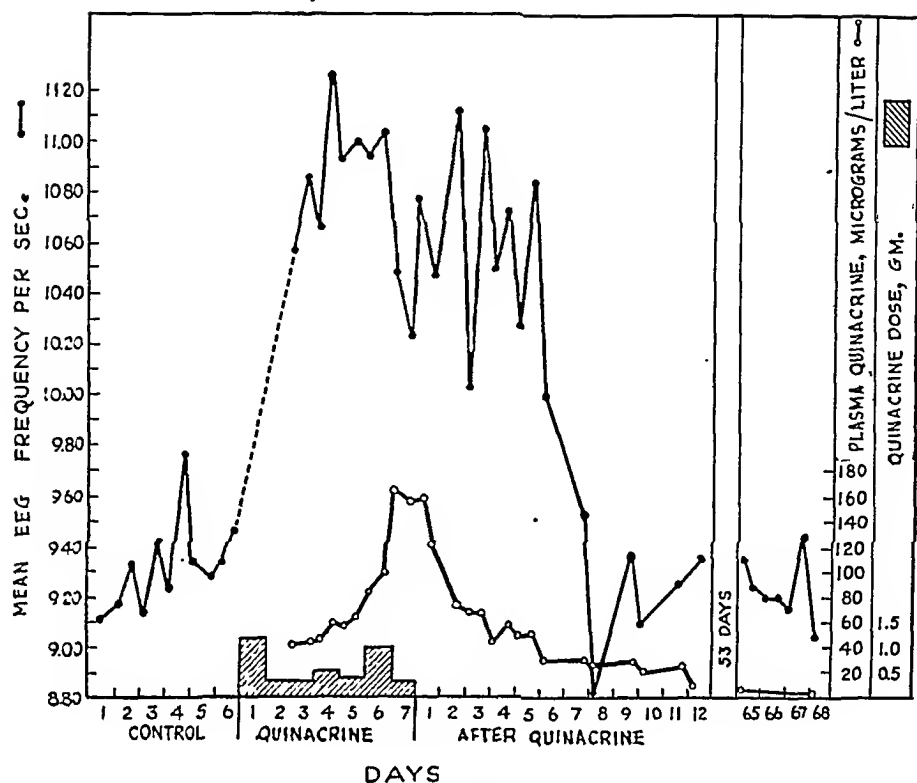


Chart 2 (subject 2).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

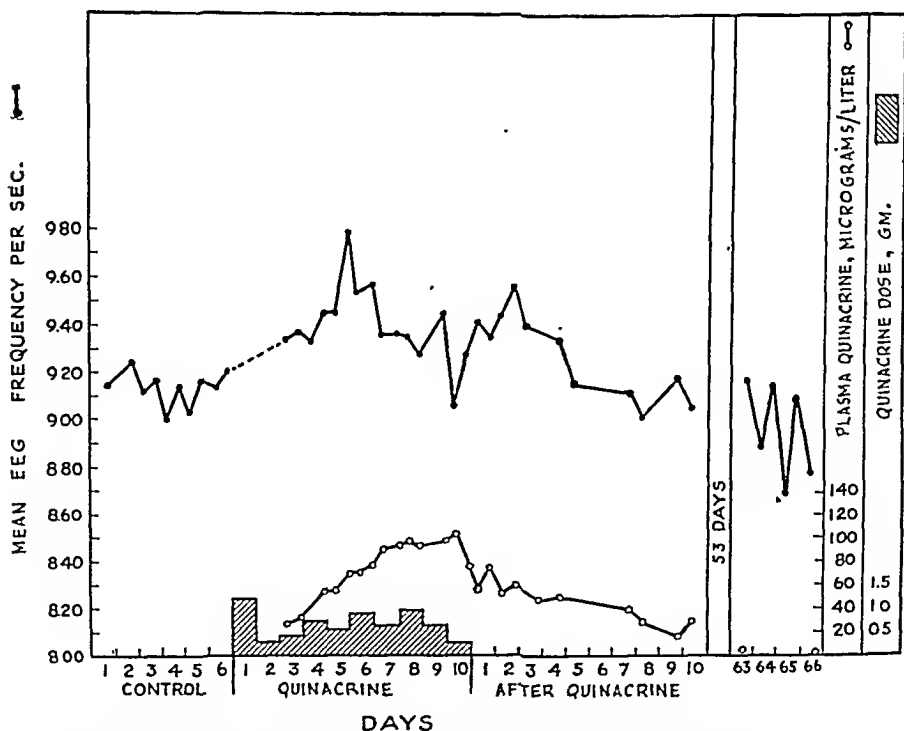


Chart 3 (subject 3).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

plasma level of the drug was 100 micrograms per liter, reached on the tenth day.

SUBJECT 4 (chart 4).—The subject, aged 35, had onset of intermittent abdominal cramps and diarrhea on the fifth day. On the seventh day sleep was disturbed by repeated terrifying dreams. He felt listless, tired and irritable but worked efficiently and under pressure. Anxiety dreams and broken sleep continued. On the tenth night he stayed awake almost all night and worked. The drug was discontinued, and these symptoms subsided over the course of the next four or five days. The maximum plasma level of quinacrine was 110 micrograms per liter, on the eighth day.

SUBJECT 5 (chart 5).—The subject, aged 29, received the drug only three days and asked that the experiment be discontinued because of unpleasant symptoms. Two days later furunculosis developed, for which he was hospitalized and treated successfully with penicillin. Symptoms during the period of quinacrine therapy consisted of malaise, headache and extreme lethargy.

Other clinical observations during the period of administration of the drug were as follows: All subjects experienced some degree of nausea, abdominal cramps and diarrhea. In all the subjects, gastrointestinal symptoms were relieved by food, and in spite of symptoms the appetite did not seem to be impaired. The body weight was measured in 1 subject (subject 4), who lost 7 pounds (3.2 Kg.) during the course of the experiment. It is probable that each subject lost some weight.

Chilly sensations, night sweats, heaviness of the legs and feet and occasional joint discomfort were experienced by 2 subjects. One of these (subject 2) had a rectal temperature of 101 to 103 F. on the seventh day, at the height of the clinical reaction. The plasma level of the drug was 162 micrograms per liter at this time, and the temperature fell to normal as soon as the drug was discontinued. Subject 5, who also had furunculosis, had a temperature of 100.8 F. three days after the drug had been discontinued; the temperatures of the remaining subjects did not exceed their maximum control levels by more than 0.5 F.

All subjects became deeply pigmented, and some pigmentation was still visible at the end of the experimental period (sixty-six days), even though the plasma level of the drug was zero at this time. The drug appeared to be excreted in the urine, feces, saliva and sweat. Two subjects noted itching. One subject (subject 4) noted the development of a lichen-like lesion on the anterior surface of the right leg, lasting about two months. Two subjects noted photophobia, and in 1 of these subjects episcleritis developed.

All the subjects agreed that the symptoms increased after each ingestion of the drug and diminished rapidly after discontinuance of the drug, even though the plasma level fell slowly. In general, the severer symptoms appeared to develop after the plasma level had reached 50 micrograms per liter.

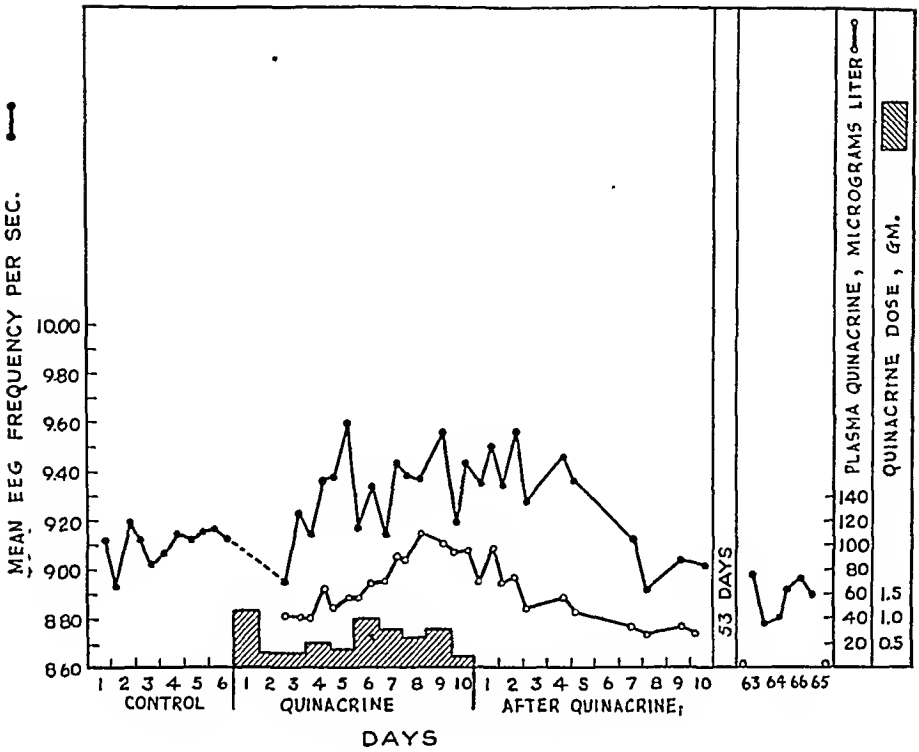


Chart 4 (subject 4).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

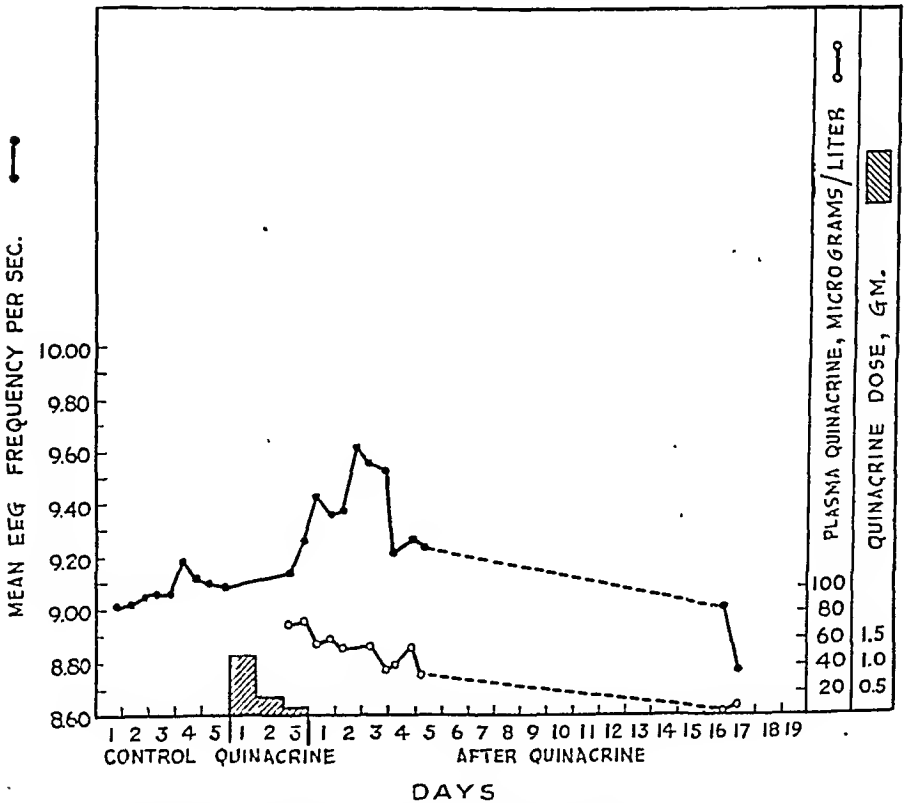
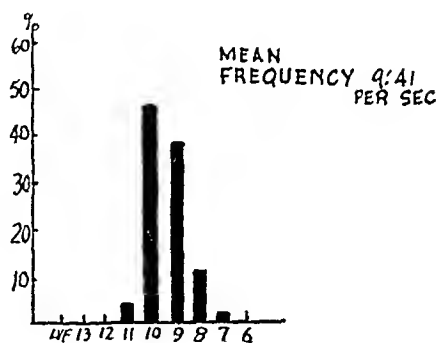


Chart 5 (subject 5).—Mean electroencephalographic frequencies and plasma levels of quinacrine during administration of the drug.

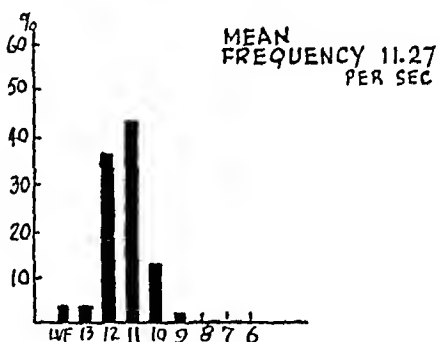
COMMENT

The clinical and electroencephalographic data obtained in this experiment constitute conclusive evidence that quinacrine acts as a stimulant to the central nervous system. The clinical symptoms included motor acceleration, restlessness, sleeplessness and increased capacity for work. Associated with this was an acceleration of the brain waves. Previous data have clearly established that, whereas depression of cortical activity

8/8/44 CONTROL



8/15/44 4 DAYS QUINACRINE: PLASMA QUINACRINE 60 MICROGRAMS/LITER



10/26/44 CONTROL; 68 DAYS AFTER QUINACRINE (PLASMA QUINACRINE, 0)

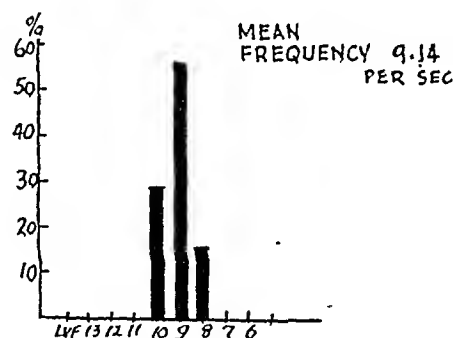
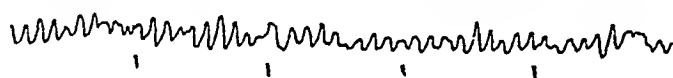


Chart 6 (subject 2).—Maximum electroencephalographic changes during administration of quinacrine hydrochloride.

is associated with slowing of the brain waves, known cortical stimulants (amphetamine, caffeine, epinephrine and camphor) produce acceleration of the brain waves.¹¹ The clinical manifestations noted in these subjects

11. Gibbs, F. G., and Maltby, G.: Effects on the Electrical Activity of the Cortex of Certain Depressant and Stimulant Drugs, *J. Pharmacol. & Exper. Therap.* 78:1 1943. Engel and Romano.² Engel, Webb and Ferris.³ Engel and Rosenbaum.^{4a} Engel, Romano and Goldman.⁵

were quite similar to those noted in patients receiving excessive doses of amphetamine or caffeine.

These results were unexpected. Clinical reports we had received led us to anticipate that the toxic psychosis noted was a delirium, in which the basic disturbance was a reduction in the level of awareness. Indeed, the first interpretation of the reaction of subject 1 was that of delirium. But the evaluation of the level of awareness and the electroencephalographic findings failed to confirm this impression. Our anticipation of delirium as the type of reaction to be expected was so great that it was only at this point that we recognized how consistent had been the behavior of the other subjects, as recorded in their daily diary. The correlation with the obvious acceleration of the electroencephalographic frequencies then became clear. Efforts to correlate this electroencephalographic change with an increase in blood sugar or in body temperature proved unsuccessful.

When the dynamics of this reaction are analyzed, the confusion with delirium becomes understandable. In delirium the basic disturbance is a reduction in the level of consciousness. The consistent slowing of the brain waves associated with this reduction has been interpreted as probably related to reduction in cortical metabolism.¹² With this reduction in consciousness and impairment of cortical function, the patient becomes less able to deal with his external environment, on the one hand, and with certain instinctual drives, on the other. There is a falling back or regression to less well integrated behavior in the intellectual, emotional and motor spheres, with a release of more primitive types of behavior, usually with much accompanying anxiety. The reaction observed with quinacrine starts out on exactly the opposite basis. There are heightened awareness, increased activity and for a while, even increased efficiency, as has already been noted empirically with amphetamine. Beyond a certain point, however, the facilitation of the free flow of ideas becomes so great that the patient is unable to cope with this bombardment. Then psychologic decompensation is to be expected. The psychologic defenses are weakened, as they are in delirium, but by a different mechanism. Excitement, panic, increase in anxiety and aggressive behavior result. This was the stage reached in subject 1. Carried one step further, it seems reasonable that were this process to continue indefinitely, especially in a person with previous deprivations, the physiologic needs of the brain might be exceeded and decompensation at a physiologic level occur. The result would be reduced awareness and delirium. Thus, the two types of clinical pictures described by Gaskill and Fitz-Hugh might be explained.

12. Engel and Romano.² Engel, Webb and Ferris.^{3a} Engel and Rosenbaum.^{4a}

The results with these 5 subjects suggest that quinacrine uniformly acts as a cortical stimulant, although it is noteworthy that the degree of acceleration of the electroencephalographic frequency did not necessarily correlate with the magnitude of the symptoms. Undoubtedly, preexistent psychologic factors also play a role. However, all our subjects showed some toxic reaction to the drug, which has not been the experience of other observers with larger series and at comparable plasma levels of the drug.¹³ Shannon has suggested that our plasma levels of quinacrine may be too low through technical error. We were unable to check this point conclusively, although a determination of the quinacrine level in several specimens by both the Masen and the Brodie¹⁴ method gave identical results. In any event, the quantity of the drug administered to our subjects was considerably in excess of that recommended for treatment of the attack, which consists of 0.2 Gm. of quinacrine hydrochloride every six hours for five doses and then 0.1 Gm. three times a day for six days, a total of 2.8 Gm. of quinacrine hydrochloride in seven days. It is certainly justifiable to conclude that in those patients who show toxic symptoms, and certainly in those who show psychic symptoms, the drug acts as a cortical stimulant. The mechanism of this action of quinacrine on the central nervous system is not clarified by these experiments, but it is noteworthy that our results can be considered consistent with observations by Waelsch and Nachmansohn¹⁵ that quinacrine is a strong inhibitor of cholinesterase. With inhibition of brain cholinesterase fast activity in the electroencephalogram is to be expected.¹⁶ In this regard quinacrine has certain properties in common with diisopropylfluorophosphate (DFP), a powerful anticholinesterase, which also produces stimulant effects on the central nervous system and the electroencephalogram.

While no special attention was directed to the problem of therapy, it would seem that a cortical depressant would be indicated. Sodium amytal seemed effective in the 1 case in which it was tried.

SUMMARY

Clinical and electroencephalographic observations were made on 5 normal adults during the administration of quinacrine hydrochloride (atabrine dihydrochloride). The daily dose ranged from 0.2 to 1.2 Gm.

13. Shannon, J. A.: Personal communication to the authors.

14. Brodie, B. B., and Udenfried, S.: The Estimation of Atabrine in Biological Fluids and Tissues, *J. Biol. Chem.* **151**:299, 1943.

15. Waelsch, H., and Nachmansohn, D.: On the Toxicity of Atabrine, *Proc. Soc. Exper. Biol. & Med.* **54**:336, 1943.

16. Forster, F. M.: Action of Acetylcholine on Motor Cortex, *Arch. Neurol. & Psychiat.* **54**:391 (Nov.-Dec.) 1946.

until the plasma level exceeded 100 micrograms per liter or until the severity of symptoms led to discontinuation. The period of administration of the drug did not exceed ten days. In all cases evidence of pronounced psychologic stimulation occurred, and the electroencephalogram showed a significant shift toward faster frequencies. These manifestations appeared by the third day and persisted for six to eight days after the drug had been discontinued, and until the plasma level had fallen to less than 40 micrograms per liter.

These data constitute evidence that quinacrine acts as a cortical stimulant.

Strong Memorial Hospital (Dr. Engel and Dr. Romano).

Cincinnati General Hospital (Dr. Ferris).

VITAMIN E IN TREATMENT OF MENTAL DISORDERS

STANLEY T. MICHAEL, M.D.

AND

ARTHUR H. RUGGLES, M.D.

PROVIDENCE, R. I.

EVIDENCE of a vitamin deficiency is usually considered a valid indication for the use of the vitamin as a therapeutic agent. No conclusive evidence of a deficiency of vitamin E has been presented in human beings. Nevertheless, this vitamin has been used in therapeutic tests and favorable results have been reported in cases of habitual abortion,¹ premature separation of the placenta,² chronic nephritis associated with hypertensive vascular disease³ and the menopausal syndrome.⁴

The advent of more potent, purified preparations has made possible intensification of research in a wider field of clinical application. Christy gave preparations of vitamin E to 25 patients with surgical menopause.

No patient was treated who did not complain of severe symptoms of vasomotor instability. The amount of the drug taken varied from 10 to 30 mg. [of ephynal acetate] a day . . . over periods of from one to six weeks. Seven patients reported complete and 16 great relief. . . . In some cases vitamin E seems more effective in relieving the symptoms of vasomotor instability than estrogens.^{4b}

The favorable results obtained by Christy in treatment of the menopause, a condition fraught with emotional disturbances ranging from neurotic complaints to frank psychotic manifestations, prompted us to test the effect of vitamin E in cases of mental disorders occurring in the involutional age period.

PRESENT STUDY

Material and Method.—Subjects were selected at random from inpatients with chronic mental disease. Later in the study patients with illnesses of recent origin and patients of a younger age group were included. Thus, a repre-

From the Butler Hospital.

1. The Vitamins: A Symposium, Chicago, American Medical Association, 1939, p. 595. Shute, E.: Vitamin E in Habitual Abortion and Habitual Miscarriage, *J. Obst. & Gynaec. Brit. Emp.* **49**:534-541, 1942.

2. Shute, E.: Vitamin E in the Prophylaxis of Abruptio Placentae, *Surg., Gynec. & Obst.* **75**:515-519, 1942.

3. Shute, E.: The Effect of Vitamin E upon Impaired Kidney Function, *Canad. M. A. J.* **52**:151-153, 1945.

4. Christy, C. J.: (a) Vitamin E in Menopause: Preliminary Report of Experimental and Clinical Study, *Am. J. Obst. & Gynec.* **50**:84-87, 1945; (b) abstracted, *J. A. M. A.* **129**:406 (Sept. 29) 1945.

Clinical Data on Patients with Mental Disorders Treated with a Preparation of Vitamin E

Case Number	Age, Years	Diagnosis	Duration of Illness, Years †	Menopause	Period of Tocopherol Therapy, Days*		Condi- tion at End of Medi- cation ‡	Vaginal Smears §		Blood Pressure	
					First Course	Second Course		Before Treatment	During Treatment	Before Treatment	At End of Treatment
Female Subjects											
1	46	Involutional psychosis, melancholia	<1	No	13	..	ss	+++	—	120/70	130/80
2	61	Involutional psychosis, melancholia	8	Yes	14	39 ^a	i	150/95	130/95
3	50	Involutional psychosis, melancholia	1	Yes	69	..	o	+++	+++	115/70	105/65
4	72	Involutional psychosis, melancholia	5	Yes	21	50	i	+++	—
5	60	Dementia precox, type undetermined	6	Yes	47	..	s	+++
6	35	Dementia precox, catatonic type	1	No	14	..	o	110/05	105/00
7	64	Dementia precox, catatonic type	37	Yes	45	..	s
8	33	Dementia precox, paranoid type	<1	Yes	20	..	o	+++	—
9	35	Dementia precox, catatonic type	1	No	20 ^a	..	ss	+++	+++
10	36	Dementia precox, mixed type	2	No	7	..	s	115/70	115/65
11	41	Dementia precox, mixed type	<1	No	28	..	r
12	26	Dementia precox, mixed type	<1	No	21	..	o	+++	+++	100/60	100/60
13	52	Dementia precox, catatonic type	<1	Yes	8	..	o
14	78	Manic-depressive psychosis, mixed type	4	Yes	63	..	o	105/65	90/60
15	42	Manic-depressive psychosis, mixed type	1	Yes	8	..	s
16	60	Psychosis with cerebral arteriosclerosis	<1	Yes	9	63	o	+++	+++	160/75	150/80
17	60	Psychosis with cerebral arteriosclerosis	5	Yes	14	..	s	+++	+++	115/75	115/65
18	36	Unclassified psychosis	1	No	36	27	i	+++	+++	135/70	155/65
19	70	Psychoneurosis; neurasthenia; alcohol and drug addiction	6	Yes	14	..	o
20	70	Psychoneurosis; anxiety state	3	Yes	13	..	s	+++	+++	150/80	145/05
21	46	Psychoneurosis; anxiety state	1	Yes	26	..	s*	+++	+++
22	68	Psychoneurosis; hypochondriasis	15	Yes	14	..	s	140/70	130/70
23	66	Psychosis with psychopathic personality; hysterical and involutional reactions	1	Yes	26	..	s	135/80	140/70
24	52	Psychosis with psychopathic personality; pathologic emotionality, hypochondriasis	1	Yes	14	..	s	+++	+++
Male Subjects											
25	61	Involutional psychosis, melancholia; early senile arteriosclerosis	15	52 ^a	..	s
26	73	Manic-depressive psychosis, depressed type	7	23 ^b	..	o
27	58	Manic-depressive psychosis, depressed type	<1	8 ^b	14 ^c	r
28	65	Psychosis with cerebral arteriosclerosis	9	17 ^b	..	s
29	63	Psychosis with cerebral arteriosclerosis	5	18	..	o
30	63	Psychosis with cerebral arteriosclerosis	<1	59 ^c	..	o	145/90	140/80
31	63	Psychosis with cerebral arteriosclerosis	7	14	..	i
32	82	Psychosis with cerebral arteriosclerosis	4	31 ^a	..	o
33	67	Psychosis with cerebral arteriosclerosis	2	79 ^a	..	i	150/85	150/80
34	73	Senile psychosis, simple deterioration	10	221 ^a	..	o	170/80	140/70
35	65	Psychosis with disease of the brain, unspecified (Pick's disease? Cerebral arteriosclerosis?)	6	23 ^b	..	o

* All subjects received 50 mg. of a preparation of mixed tocopherols ("tofaxin") daily except where indicated. In this column, a, means administration on alternate days; b, administration twice daily; c, administration of "ephynal acetate" 10 mg., three times a day, and e, administration of "ephynal acetate," 30 mg., twice daily.

† <1 indicates duration of the illness of less than one year.

‡ In this column, r indicates remission; i, improvement; s, stimulation, psychomotor activity; ss, condition worse, and o, no change.

§ Vaginal smears are graded on the scale of +, +++, + (severe estrogenic deficiency) to +, +, + (full estrogenic activity).

sentative cross section of various mental disorders in hospitalized patients was obtained. A total of 35 patients were studied of whom 24 were women and 11 men. The duration of the illness of 16 patients was one year or less. Of these, 12 were experiencing their first mental illness. All subjects were studied in the controlled environment of the hospital.

The predominant pattern of medication was 1 capsule of a commercial preparation ("tofaxin") containing 50 mg. of mixed (alpha, beta and gamma) tocopherols, of which 30 mg. was alpha tocopherol,⁵ given over periods ranging from seven to one hundred and twenty-one days with various patients. In several instances, 1 capsule was given twice daily, or only on alternate days, to test the effect of different doses. "Ephynal acetate" (alpha tocopherol acetate) was used for several male patients in doses of 10 mg. three times daily. Estrogenic levels were determined in 7 female subjects before institution of treatment and after two weeks of medication with the vitamin E preparation by the vaginal smear method of Shorr⁶ and Salmon and Frank.⁷ On the basis of results obtained for the first few patients who underwent therapeutic tests with the vitamin E preparation, we included determinations of the blood pressure to test the possible association of increase in blood pressure with the observed increase in psychomotor activity resulting from the drug.

The diagnoses for the patients studied, their ages, the duration of their illness, the duration of medication and dosage employed and other facts pertaining to the method and results of study are assembled in the accompanying table.

Results.—Two patients (11 and 27 in the table) experienced a complete remission with administration of the preparation of tocopherols and were discharged home. One of these (27), relapsed in two weeks after discontinuation of treatment and returned to the hospital. While he benefited somewhat from a repetition of vitamin E medication, he experienced a complete and enduring remission from electric shock and a change in vocation.

Five patients (2, 4, 18, 31 and 33) showed definite improvement, not leading to complete remission or to discharge from the hospital. Interruption of medication of patients 2 and 18 resulted in a partial relapse. Resumption of the treatment over a prolonged period did not lead to further improvement, beyond that obtained in the first course of medication. The common features of the illnesses of the patients who showed improvement were depression, agitation and anxiety, with moderate confusion and blocking of speech.

Increased psychomotor activity during medication with tocopherols was observed in 14 patients. The change in 12 of these patients consisted in mere intensification of the patient's old symptoms, with no

5. "Tofaxin" was supplied by the Winthrop Chemical Company, Inc., through the courtesy of Mr. Shephard M. Crain.

6. Shorr, E.: New Technic for Staining Vaginal Smears: Single Differential Stain, *Science* **94**:545-546, 1941.

7. Salmon, U. J., and Frank, R. T.: Hormonal Factors Affecting Vaginal Smears in Castrates and After Menopause, *Proc. Soc. Exper. Biol. & Med.* **33**:612-614, 1936.

new symptoms. Two of these 14 patients (1 and 9) became definitely worse during medication with tocopherols, exhibiting new symptoms. Both patients were given the drug shortly after admission, in an acute phase of development of their illness; it is possible that their illness would have become worse regardless of medication. The net result of administration of tocopherols in this group of 14 patients was an aggravation of clinical behavior. The most prominent changes in behavior in these patients were an increase in somatic, neurotic or hypochondriacal complaints; a restless and interrupted pattern of sleep; increased agitation; an increased need to discuss personal problems, and, in 1 instance, assaultiveness. Owing to this form of undesirable stimulation, the planned minimum course of two weeks of medication with the vitamin E preparation was shortened in several cases.

In most instances in which the patient showed improvement or increased psychomotor activity, a change in behavior was noticeable after three or four doses (accumulated 150 to 200 mg.) of a vitamin E preparation. After discontinuation of medication, the increase in psychomotor activity abated within a few days, except for the 2 patients (1 and 9) described in the preceding paragraph, who continued to show a downward trend in their illness.

No appreciable change was observed in the remaining group of 14 patients (table).

Four patients (3, 8, 21 and 24) complained of menopausal symptoms of a vasomotor type. One of these (patient 3) reported complete relief from vasomotor symptoms; the remaining 3 patients had partial relief. None of these patients showed improvement in mental condition. The subject who was completely relieved of menopausal symptoms made a determined attempt at suicide on the forty-fifth day of continuous medication with tocopherols.

Estrogenic activity determined in 7 subjects by the vaginal smear method showed no appreciable change in 5 patients after two weeks of medication with tocopherols. A moderate decrease in estrogenic level was observed in 2 subjects.

Increase in blood pressure, anticipated on the basis of psychomotor activity in a number of patients, did not occur. A trend toward transitory reduction in both systolic and diastolic blood pressure was observed several days after beginning of medication with tocopherols in 3 patients with arteriosclerosis.

Five patients of this series subsequently recovered with other methods of treatment and left the hospital. Three patients (1, 3 and 27) had a satisfactory remission following electric convulsive treatment. One patient (8) recovered after ambulatory subshock insulin therapy, and 1 patient (21) showed a satisfactory remission with psychotherapy.

COMMENT

The conditions treated and the doses of concentrated preparations of tocopherols used in these studies indicate the possibility that the therapeutic effect is achieved not by correction of a deficiency of vitamin E, but, rather, by a pharmacodynamic effect beyond that of a catalytic function, usually ascribed to vitamin substances. The patients tested in these studies came from financially well endowed families and probably had received sufficient nourishment before admission to the hospital. While in the hospital, the patients received an adequate diet; in addition, many subjects of this study were receiving adequate doses of polyvitamin preparations before inception of and during the study. It may be assumed that they did not have a deficiency of the commonly known vitamins. To the best of present day knowledge, the menopausal symptoms of the patients of Christy,^{4a} which occurred after operative removal of the gonads, cannot be ascribed to a deficiency of vitamin E. We assume, therefore, that the beneficial effects of tocopherols in the menopausal syndrome and the effects observed in our patients are due not to correction of a vitamin deficiency, but, rather, to a drug effect of tocopherol.

The general effect of tocopherols in our patients seemed to be that of stimulation. The stimulative effect was observed in 60 per cent of our patients. The effect on behavior was evidently dissociated from the beneficial effect on the menopausal vasomotor disturbances in the few patients whom we were able to test. The results of discontinuation and resumption of the medication with tocopherols in 4 patients in whom we observed improvement lead us to believe that the improvement in their mental condition was associated with the administration of tocopherol. The obvious increase in psychomotor activity in 12 patients, several of whom had chronic illnesses and had been under observation over a considerable period, coincided remarkably with administration of tocopherols, an observation which, to us, again indicates that the vitamin E preparation was the cause of the change in behavior.

SUMMARY AND CONCLUSIONS

The vitamin E preparations (tocopherols) used in these studies had a perceptible influence on psychomotor activity of mentally ill patients in 60 per cent of the cases studied. The observed effect was of the nature of stimulation, resulting in clinical improvement in 20 per cent of the subjects and in clinical intensification of symptoms in 40 per cent. No appreciable change in behavior was observed in the rest. The beneficial results were most obvious in patients whose illness was characterized chiefly by depression, agitation, anxiety and decreased ability for verbalization.

The number of complete remissions following medication with tocopherols was not significantly greater than that of the expected spontaneous remissions.

The value of tocopherol (vitamin E) as a therapeutic agent in cases of mental disorders ranks below that of accepted shock treatments. Preparations of vitamin E, however, may have some value in the conservative management of depressed mental patients for whom shock therapy is contraindicated.

The described effects of vitamin E therapy are considered to be due to a drug effect of tocopherol rather than to correction of a deficiency of vitamin E.

Butler Hospital.

SODIUM AMYTAL IN TREATMENT OF APHASIA

LOUIS LINN, M.D.

NEW YORK

WHILE on military duty in North Africa in 1943, Stein and I¹ had the opportunity to observe the effects of intravenous administration of sodium amytal on a group of patients with dysphasia following shell fragment wounds of the dominant cerebral hemisphere. It was found that motor aphasia improved suddenly and dramatically in response to this medication. It was observed, too, that in some cases this improvement was sustained long after the effects of the sodium amytal had worn off. Furthermore, during the period of work with the patient, the helpless frustration reactions so commonly observed in aphasic patients did not appear and the patient was capable of sustained effort far beyond that which he showed without the drug. For these reasons, it was felt that the drug would be useful in the rehabilitation of soldiers with aphasia due to cerebral injuries. These observations have been verified by other investigators; in some cases the drug has had the anticipated beneficial effect.

Since returning to civilian practice, I have been able to demonstrate the usefulness of this drug. Since the civilian physician has relatively little contact with military medical literature, a brief note bringing the matter to the attention of a wider circle of medical readers seemed advisable. The following 2 cases illustrate the effects of sodium amytal in aphasia.

REPORT OF CASES

CASE 1.—R. H., a woman aged 40, experienced right hemiplegia associated with mixed aphasia after operation for a meningioma involving the left temporo-parietal region. She responded to her aphasia with incapacitating emotional outbursts. In conversations she was quickly exhausted and discouraged.

She was given a simple group of tests to perform. First, she had to name five objects (fork, soap, pencil, rubber eraser, light bulb). Second, she had to indicate by word or action what these objects were used for. Third, she was given the Goldstein-Scheerer block test. The performance in each situation was recorded in detail. Then a 5 per cent solution of sodium amytal was injected slowly intravenously. After she had received about 4 cc., the patient displayed a sudden change in mood, which indicated that the optimum end point of the injection had

From the Neurological Service of the Mount Sinai Hospital.

1. Linn, L., and Stein, M.: The Use of Sodium Amytal in the Treatment of Aphasia, *Bull. U. S. Army M. Dept.* 5:705 (June) 1946.

been reached. Instead of her usual irritable, discouraged, querulous manner, she became cheerful and relaxed. She spoke spontaneously and easily. The foregoing tests were repeated. Her performance was strikingly improved. She succeeded in completing in a few seconds tasks which previously took minutes of painful, futile struggle. A striking feature of the performance following the injection was her ability to sustain over a long period of time her attention and energy output. She left the hospital shortly after this one observation, and it was not possible to carry out further tests with her.

CASE 2.—R. W., a woman aged 47, on Nov. 23, 1945 had sudden onset of right hemiplegia with aphasia. A diagnosis of cerebral thrombosis was made, and she was admitted to Mount Sinai Hospital. The hemiplegia cleared up in a short time, but the aphasia persisted. The patient was practically mute. She was given an intravenous injection of sodium amytal in the manner described in the first case. A striking improvement in her speech resulted. However, as the effect of the drug wore off she lapsed into her previous state of mutism. With repeated injections, the ability of the drug to produce this transitory improvement was gradually lost. At this time the patient is, once again, practically mute.

COMMENT

This material is presented as a brief note for the purpose of bringing promptly to the attention of a wider circle of physicians this interesting and useful procedure. It has long been known that many cases of impairment in cerebral function have an emotional overlay. The aphasic person who cannot speak the words of a verse can sometimes sing them, and in response to sufficient emotional pressure may be able to utter expletives which he cannot speak as single words. The patient with paralysis agitans who is rigid and bent has been known to become capable of performing acts requiring considerable agility under certain conditions.

Obviously, sodium amytal does not reverse an organic process. However, its use in the manner described not only may make it possible to hasten the rehabilitation of patients with post-traumatic aphasia, but may afford opportunities to explore the psychologic component in many apparently hopeless cases of organic disease of the brain.

70 East Eighty-Third Street (28).

Case Reports

SUBARACHNOID CERVICAL ANGIOMA WITH CUTANEOUS HEMANGIOMA OF A CORRESPONDING METAMERE

Report of a Case and Review of the Literature

CAPTAIN GLEN O. CROSS, MEDICAL CORPS, ARMY OF THE UNITED STATES

THE WIDER recognition of the relationship between developmental anomalies of the skin and coexisting abnormalities of other ectodermal derivatives, particularly the nervous system, is important clinically. Early surgical relief when such lesions are compressing the adjacent structures of the central nervous system is imperative, and too long a delay causes irreparable damage. This has been repeatedly emphasized by a number of authors. As early as 1895 Berenbruch¹ noted the relation of cutaneous angiomas, lipomas and vascular tumors of the spinal cord. He was able to demonstrate actual vascular connections between an angioma of the cervicothoracic portion of the spinal cord and multiple angioliipomas of the skin of the upper part of the trunk in a case reported at that time, the connecting vessels in that instance passing by way of the intervertebral foramens. Cushing and Bailey,² in their monograph on vascular tumors, pointed out that the skin and other organs lying in the same segment of nerve distribution are often affected when a vascular abnormality of the central nervous system exists. He reported nevi of the face associated with intracranial vascular tumors. There have been numerous subsequent reports of similar lesions; however, according to Turner and Kernohan,³ instances of vascular tumors of the cord associated with nevi of the corresponding cutaneous segments were reported only four times prior to 1941. The first report of that nature was one by Cobb⁴ in 1915. He collected 7 cases of subdural angioma from the literature, 1 of which was Berenbruch's previously mentioned case. The latter was the only case with associated cutaneous nevi. Rand,⁵ in 1927, described a case of hem-

From the Neurosurgical Section, Letterman General Hospital, San Francisco.

1. Berenbruch, K.: Ein Fall von multiplen angioliipomen kombiniert mit einem Angiom des Rückenmarks, *Deutsche Ztschr. f. Nervenhe.* **6**:127-136, 1895.

2. Cushing, H. W., and Bailey, P.: *Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas*, Springfield, Ill., Charles C Thomas, Publisher, 1928.

3. Turner, O. A., and Kernohan, J. W.: Vascular Malformations and Vascular Tumors Involving the Spinal Cord, *Arch. Neurol. & Psychiat.* **46**:444-463 (Sept.) 1941.

4. Cobb, S.: Haemangioma of the Spinal Cord Associated with Skin Naevi of the Same Metamere, *Ann. Surg.* **62**:641-649, 1915.

5. Rand, C. W.: Hemangioma of the Spinal Cord, *Arch. Neurol. & Psychiat.* **18**:755-765 (Nov.) 1927.

angioma with an associated nevus of the back. . In Johnston's⁶ case, reported in 1938, an epidural hemangioma of the spinal cord was associated with a cutaneous nevus over the tenth rib posteriorly. The next case was reported by Karshner, Rand and Reeves⁷ in 1939. If Berenbruch's case is included as the first one to be reported, a total of 5 cases was reported prior to the present case. The distribution of the "external sign posts" (Cushing and Bailey²) in the aforementioned cases is shown in figure 1. It will be seen that the present case is the only one with a cutaneous lesion of the cervical region. This is interesting in view of the report of Ward and Covington,⁸ that the nape of the neck is the most frequent location for superficial hemangiomas of the skin. This observation is supported by the studies of Watson and McCarthy⁹ on a series of 1,056 cases of hemangioma of the skin. They reported that 50 per cent of these lesions occurred in the region of the neck, although this area makes up less than one seventh of the total body surface. Rasmussen, Kernohan and Adson,¹⁰ reporting on a series of 557 tumors of the cord, found 52 to be tumors of blood vessels, with 19 per cent located in the cervical, 64 per cent in the thoracic and 17 per cent in the lumbar region. This would help to explain the rarity of the association of hemangiomas of the skin of the neck with vascular abnormalities of the cervical portion of the cord, as the abnormalities of the cord are comparatively rare in that locale. Turner and Kernohan,³ in their study of 46 cases of vascular tumors of the spinal cord, which included 18 cases of angioma, stated that in no case was there any cutaneous vascular or pigmented nevus. Cobb,⁴ in his report, referred to a case of a large angioma of the right flank, associated with clinical signs of tumor of the cord, which terminated fatally; but as no operation or postmortem examination was made he did not include this case in his series. Elsberg¹¹ referred to a case reported by Alexander in 1922. No reference was found in the literature of that time to this publication. Reported instances of hemangioma of the vertebral bodies associated with angiomas of the skin were found.

6. Johnston, L. M.: Epidural Hemangioma with Compression of the Spinal Cord, *J. A. M. A.* **110**:119-122 (Jan. 8) 1938.

7. Karshner, R. G.; Rand, C. W., and Reeves, D. L.: Epidural Hemangioma Associated with Hemangioma of the Vertebrae, *Arch. Surg.* **39**:942-951 (Dec.) 1939.

8. Ward, G. E., and Covington, E. E.: Hemangiomas of the Skin, *J. A. M. A.* **114**:2069-2075 (May 25) 1940.

9. Watson, W. L., and McCarthy, W. D.: Blood and Lymph Vessel Tumors, *Surg., Gynec. & Obst.* **71**:569-588 (Nov.) 1940.

10. Rasmussen, T. B.; Kernohan, J. W., and Adson, A. W.: Pathological Classification with Surgical Consideration of Intraspinal Tumors, *Ann. Surg.* **111**:513-530 (April) 1940.

11. Elsberg, C. A.: *Tumors of the Spinal Cord*, New York, Paul B. Hoeber, Inc., 1925, pp. 203-205.

Ferber and Lampe¹² recorded a case in which there were many small hemangiomas of the skin of the back and abdomen in the region of the fifth to the tenth thoracic spinal segments, with corresponding neurologic signs. There was roentgenographic evidence of hemangioma of the seventh thoracic vertebra with obstruction of the spinal canal and compression of the cord. The patient was successfully treated with roentgen radiation. Topfer¹³ studied 2,154 cadavers, in 256 of which (about 12 per cent) he observed hemangiomas of the vertebrae associated with lipomas of the skin in corresponding metameres. Elsberg¹⁴ stated that he operated in a case in which a large mass of fat filled with dilated veins was observed in the subcutaneous fat of the

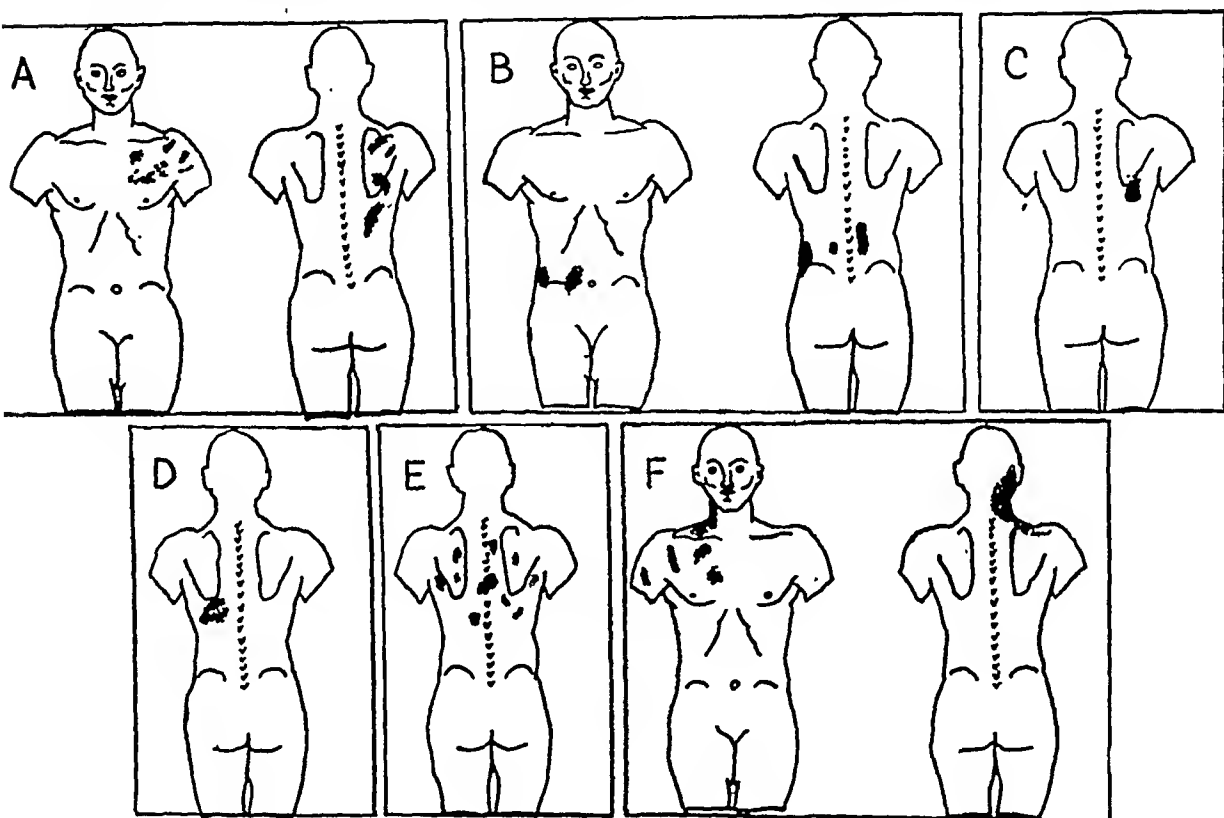


Fig. 1.—Distribution of the cutaneous angiomas in the cases reported in the literature. *A*, Berenbruch's case (1895); *B*, Cobb's case (1915); *C*, Rand's case (1927); *D*, Johnston's case (1938); *E*, Karshner, Rand and Reeve's case (1939); *F*, present case.

back overlying a spinal varicosity of the fourth thoracic segment. Blackford,¹⁵ in 1943, reported a case of hemangioma of the eleventh thoracic

12. Ferber, L., and Lampe, I.: Hemangioma of the Vertebrae Associated with Compression of the Cord, *Arch. Neurol. & Psychiat.* **47**:19-29 (Jan.) 1942.

13. Topfer, cited by Karshner, Rand and Reeves.⁷

14. Elsberg, C. A.: *Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Its Membranes*, Philadelphia, W. B. Saunders Company, 1916.

15. Blackford, L. M.: Hemangioma of the Vertebrae with Compression of the Cord, *J. A. M. A.* **123**:144-146 (Sept. 18) 1943.

vertebra associated with a tumor 4 cm. in diameter, protruding 2 to 3 cm. over the right half of the vertebra. This tumor was said to "look and feel like a mass of tangled veins." Ehni and Love¹⁶ reviewed the literature up to 1945 and reported 29 cases of intradural lipoma. Five of their series of extradural tumors were classified as "angioliipoma"; 1 was called "angioma with fat cells," and 1 a "vascular lipoma." In 5 of the total series lipomas occurred in corresponding segments of the skin. In their discussion of these cases they mentioned the possibility that lipoma and angioma are related neoplasms and stated:

. . . This brings to mind the case reported by Cobb [4] . . . These cases seem to indicate the participation of common mesenchyme with an abnormal potentiality for the formation of tumor in the genesis of the pia.

They summarized their study by saying:

. . . Neurofibromatosis has been related to Lindau's disease and to Sturge-Weber disease, and the group of diseases has been termed congenital ectodermosis. . . There appear to be reasons for including multiple lipomatosis in the group [of phacomatosis]. . . There is a close relation between angioma and lipoma. Intraspinial lipoma appears to be related to neurofibromatosis and the other "phacomatoses."

Cushing and Bailey² called attention to Lindau's belief that the hemangioma of the cerebellum was part of a more generalized systemic disorder, which he called "angiomatosis of the central nervous system," and that it was often accompanied with cystic formations in the pancreas, kidneys, liver and testes and, more rarely, with hypernephroma.

It would seem to be accepted that vascular tumors of the spinal cord are but part of a widespread process. In the cases discussed here the tumor of the spinal cord was discovered because it presented symptoms and was associated with vascular abnormalities of the skin, while other developmental anomalies which may have been present were asymptomatic.

REPORT OF CASE

History.—On Oct. 3, 1944, a Mexican aged 19, a soldier, was admitted to a station hospital overseas with complaints of weakness of the left arm and leg and pain in the right leg. His past history revealed that he had previously been hospitalized in December 1943 because of persistent sharp pains in the right ankle. There was noticeable weakness of the left arm at that time. As no apparent cause for his symptoms was then found, he was discharged to return to duty. In May 1944, after a period of progressive ascent of the pain in the right leg, there developed severe pain in the right hip and iliac region. Because appendicitis was suspected, he was hospitalized; but the diagnosis was not confirmed, and he was again returned to duty. For two months prior to his last admission to the hospital he had noticed progressive difficulty on arising in the morning because of pain in the right leg and stiffness of the left leg and arm. He stated that the left leg

16. Ehni, G., and Love, J. G.: Intraspinial Lipomas, Arch. Neurol. & Psychiat. 53:1-28 (Jan.) 1945.

and hand seemed to be "wasting away." Examination on October 3 revealed beginning clawhand on the left. There were almost complete loss of grip in this hand, and atrophy of the musculature of the left arm was estimated at 50 per cent. No sensory abnormalities were elicited. The left leg showed loss of muscular power and "20 per cent atrophy." The deep reflexes were hyperactive, but no pathologic toe signs were observed. There was an exhaustible ankle clonus on the left. Laboratory studies at that hospital revealed no abnormalities. He was sent to a general hospital on October 11 with a diagnosis of "hemiplegia, left, incomplete, cause undetermined." Examination at that hospital revealed, in addition, bilaterally hyperactive knee jerks and a positive Babinski sign on the left, and

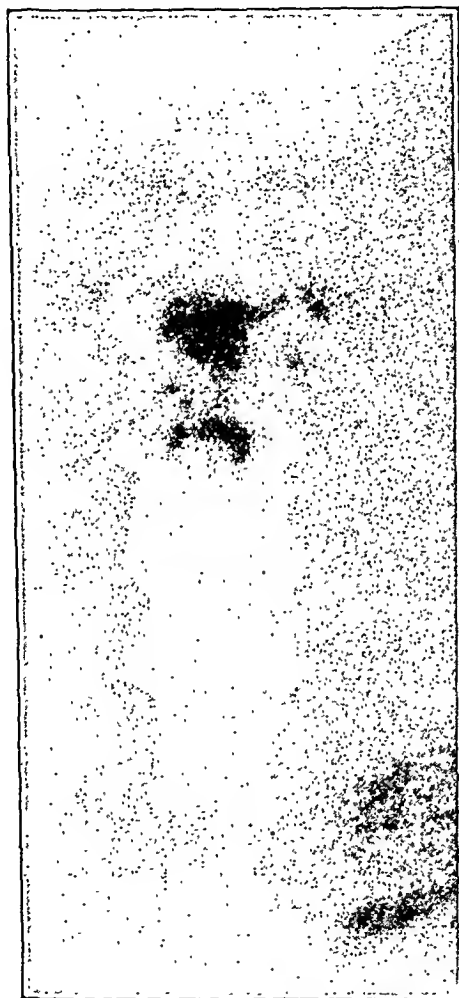


Fig. 2.—Myelogram showing almost complete block at the interspace between the fifth and sixth cervical vertebrae.

lowered cutaneous temperature over the left upper and lower extremities. Fibrillations were observed in the musculature of the left thigh. Paresthesias to pinprick were noted over the left lower extremity. A laboratory survey, including roentgenograms of the complete vertebral column, studies of the spinal fluid and its dynamics and gastric analysis, revealed no pathologic condition. He was returned to the United States with the tentative diagnosis of "amyotrophic lateral sclerosis" and was admitted to the DeWitt General Hospital on April 14, 1945.

Examination.—In addition to the signs already recorded, the patient presented a hemangioma of the skin of the left side of the neck and prominent vascular

markings of the skin of the upper part of the chest and over the seventh cervical and first thoracic vertebral spines. The biceps and triceps reflexes were more active on the left side than on the right. The abdominal and cremasteric reflexes were absent on the left side. There were a positive Hoffmann sign and a classic left Babinski sign on the left side. There was perversion of sensation over the left side of the body, described as "a feeling like an electrical shock," when the skin was stroked with a pinpoint. Position sense was lost in the left great toe. Vibratory sense was normal. The body temperature was higher on the right side than on the left. There were mild hypesthesia of the right side of the face and hypes-



Fig. 3.—Exposure of the hemangioma in the cervical region.

thesia of the left side of the palate, and the uvula drew up to the right. There was a congenital coloboma of the left iris. No hemangiomas were seen in the retina, and the disks were normal.

Laboratory Studies.—The blood count revealed 5,000,000 red cells; 90 per cent (15 Gm. per hundred cubic centimeters) hemoglobin, and 7,000 white cells, with a differential count of 1 basophil, 3 eosinophils, 49 segmental forms, 44 lymphocytes and 3 mononuclear cells. The hematocrit reading was 44. The sedimentation rate was 1 mm. in one hour. The Kahn reaction of the blood was negative. The urine was cloudy and yellow, with a specific gravity of 1.021 and an acid reaction.

Spinal puncture and manometric study of the spinal fluid, done after the method of Grant and Cone, indicated a subarachnoid block. The total protein of the spinal fluid was 28.5 mg. per hundred cubic centimeters.

In view of the neurologic findings and the manometric readings, with the presence of the hemangioma of the skin, the possibility of a hemangioma of the upper cervical portion of the cord was considered. A myelogram, taken with 6 cc. of "pantopaque" (a mixture of ethyl esters of isometric iodophenylundecylic acid), showed almost complete block of the canal at the interspace between the fifth and sixth cervical vertebrae (fig. 2).

Operation (Dr. Frank Echlin).—With the use of endotracheal anesthesia, a laminectomy was done on the fifth, sixth and seventh cervical vertebrae. The dura was opened, and an extensive mass of subarachnoid blood vessels was seen. These vessels extended upward to the upper limits of the dural opening. The laminectomy was extended to the second cervical vertebrae, and the dura was opened as far as the atlas. The varix was seen to extend beneath the lamina of the axis into the posterior fossa. The vessels were of mixed arterial and venous type. The vascular mass was so dense that the cord could not be seen except below the sixth cervical segment. The cord at that level appeared compressed and flattened. The large blood vessels measured up to 4 cm. in diameter and were continuous with the vessels in the spinal cord.

Because the upper extent of the vessels could not be determined and because of the continuity of the vessels with those of the cord, no attempt was made to remove the varix, in view of the danger of development of transverse myelitis. The question of placing a fascial transplant in the dura to decompress the varix was considered, but the dura could be closed over the varix, leaving approximately $\frac{1}{2}$ inch (1.3 cm.) of space between the vessels and the dura posteriorly. The dura was accordingly closed, and the other tissues were closed in layers over the wound.

Postoperative Course.—Recovery was uneventful. The patient was relieved of the pain in the right arm and leg. He was furnished with a brace for the neck and was ambulatory in three weeks. He was then given high voltage roentgen therapy to the posterior portion of the neck, receiving 1,400 r over a period of eight days. This did not alter his clinical picture to any appreciable degree, possibly because of the large size of the vessels. A reinfection type of pulmonary tuberculosis then developed, and the patient was transferred to a veterans administration facility.

COMMENT

The progress of the symptoms in this case followed the course presented by Oppenheim and Frazier¹⁷ for extramedullary tumors of the spinal cord. They divided the signs and symptoms into three phases: (1) involvement of the nerve roots (pain); (2) beginning compression of the spinal cord (motor weakness), and (3) extreme compression of the spinal cord (paralysis and transverse myelitis). Globus and Doshay,¹⁸ in their discussion of 42 cases of vascular tumors of the cord, describe pain as the most frequent early sign. It was

17. Oppenheim and Frazier, cited by Rasmussen, Kernohan and Adson.¹⁰

18. Globus, J. L., and Doshay, L. J.: Venous Dilatations and Other Intraspinal Vessel Alterations Including True Angiomata with Signs and Symptoms of Cord Compression, Surg., Gynec. & Obst. 48:315-366 (March) 1929.

present in 46 per cent of their cases as the first symptom. Motor weakness was present in 12 of their cases, while paresthesia was a feature in only 3 cases. In contrast to the myelographic findings in the present case, Globus and Doshay¹⁸ stated that in their series studies made in a few cases with iodized poppyseed oil revealed no block. Delmas-Marsalet,¹⁹ however, described a "characteristic appearance" of hemangiomas of the cord in the myelogram. Elsberg¹¹ pointed out that the signs and symptoms of spinal varices are sometimes indistinguishable from those produced by tumors of the cord and cautioned against always accepting the varices as the sole lesions without looking for a tumor or other lesion at a higher level which may be causing venous obstruction and dilatation.

SUMMARY

A case of hemangioma of the cervical portion of the spinal cord associated with cutaneous hemangiomas of the corresponding metameres is presented.

The 5 previously reported cases are reviewed.

The apparent close relationship of the various abnormalities of development of the ectodermal derivatives and the importance of their clinical recognition are stressed.

19. Delmas-Marsalet, P.: Poussées évolutives gravidiques et image lipiodolée caractéristique des hémangiomes médullaires, *Presse méd.* **49**:964-965 (Sept. 10-13) 1941.

News and Comment

RESIDENCY TRAINING PROGRAMS OF VETERANS ADMINISTRATION

Two new residency training programs for physicians desiring to train in neurology under the Veterans Administration have been organized. The residencies are designed to prepare residents for certification in neurology by the American Board of Psychiatry and Neurology.

The first new program will be conducted under the auspices of the New York University and the neurologic service of the Psychiatric Division of the Bellevue Hospital, New York. The program provides for training at Bellevue Hospital and the Veterans Administration New York Regional Office. The staff includes Dr. S. Bernard Wortis, Dr. E. D. Friedman, Dr. Lewis Stevenson, Dr. Samuel Brock, Dr. M. B. Bender and Dr. Margaret Kennard. Applications should be sent to Dr. S. Bernard Wortis, chairman, Deans Subcommittee for Neurology, New York University, 400 East Thirtieth Street, New York.

The second new program has been organized by the George Washington School of Medicine and the Georgetown University School of Medicine. Residents will be offered training facilities at the Veterans Administration Hospital (Mount Alto), Washington, D. C.; Gallinger Municipal Hospital, the Veterans Administration Regional Office, Children's Hospital and the Army Institute of Pathology. The staff includes Dr. Walter Freeman, Dr. Norman Q. Brill, Dr. James Watts, Dr. Webb Haymaker, Dr. Paul Chodoff, Dr. Harold Stevens and Dr. Othmar Solnitzky. Applications should be forwarded to Dr. Walter Freeman, chairman, Deans Subcommittee for Neurology, 2014 R Street, Northwest, Washington, D. C.

Other medical schools affiliated with the Veterans Administration for residency training in neurology where training programs are already under way, are:

Medical School	Location of Veterans Administration Hospitals and Clinics	Applications Received by
Cornell University Medical College... Columbia University College of Physicians and Surgeons	Bronx, N. Y.	Dean Willard C. Rappleye, 630 West One Hundred Sixty-Eighth Street, New York
Northwestern University Medical School University of Illinois College of Medicine	Ehnes, Ill.	Dr. Lewis J. Pollock, Northwestern University Medical School, Chicago
University of Minnesota Medical School	Minneapolis	Dean Harold S. Diehl, University of Minnesota Medical School, Minneapolis 14
Boston University School of Medicine Tufts College Medical School Harvard Medical School	Framingham, Mass.	Dr. Harry C. Solomon, Chairman, Deans Subcommittee for Neuropsychiatry, Harvard Medical School, Boston
Jefferson Medical College of Philadelphia	Coatesville, Pa.	Dr. Edward A. Streeker, Chairman, Deans Subcommittee for Neuropsychiatry, 111 North Forty-Ninth Street, Philadelphia 39

ADOLF MEYER GIFT TO SETON INSTITUTE

The Medical Advisory Board of the Seton Institute and the Sisters of Charity of St. Vincent de Paul are pleased to announce the gift from Dr. Adolf Meyer of his entire personal collection of neuroanatomic and neuropathologic material, consisting of some sixty large boxes of serial sections from crucial human case

material, as well as material of a comparative nature. Included in the gift is an exhaustive card index file of neurologic subjects.

The Seton Institute plans to use this material as the nucleus about which to develop a laboratory for the study of neuroanatomy, neurophysiology and neuropathology.

The material will soon be in available form for the instruction of candidates for the American Board examinations in neurology.

The institute is deeply indebted to Dr. Meyer for this magnificent gift, and in recognition of his generosity the laboratory will be named the Adolf Meyer Laboratory of Neurology.

SOUTHERN PSYCHIATRIC ASSOCIATION

The officers and fellows of the Southern Psychiatric Association announce that their annual meeting will be held in Birmingham, Ala., on Oct. 13 and 14, 1947.

AMERICAN BOARD OF NEUROLOGICAL SURGERY

On June 3, 1947 Dr. William J. German, 310 Cedar Street, New Haven, Conn., was elected secretary-treasurer of the Board, to replace Dr. Paul C. Bucy, Chicago, whose term of office has expired.

WARTIME TRAINING CREDIT ALLOWED BY THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

In order to avoid misunderstanding regarding the allowance of one year of training credit for work in the armed forces during wartime, it should be noted that wartime to this Board means V-J Day plus six months.

Therefore, men who entered the service on V-J Day would be allowed six months' credit. Men who entered the armed forces after February 1946 will not be granted credit toward the training requirements unless they were residents in hospitals approved by this Board for residency training. If they have practiced psychiatry or neurology during this time, however, it is probable that this will be counted toward the requirements for experience.

F. J. BRACELAND, Secretary-Treasurer.

THE WOODS SCHOOLS TO BECOME A NONPROFITABLE, CHARITABLE CORPORATION

Mrs. Mollie Woods Hare, founder and active head of the Woods Schools, Langhorne, Pa., applied on June 9, 1947, to the Bucks County Court, at Doylestown, Pa., to make an outright gift of the \$2,500,000 school property to a non-profitable, charitable corporation. The corporation, to be known as The Woods Schools, is to be administered by a self-perpetuating board of trustees from five to fifteen members.

The school was founded thirty-one years ago for the express purpose of teaching the exceptional child—the child who, for whatever reason, does not fit into the usual educational program. Throughout its entire existence the school has concentrated on this field of education, with consistently successful results. It has always maintained extremely small classes so as to give personal attention to each student. For the last thirteen years it has conducted the internationally known Child Research Clinic with an advisory board of outstanding medical and educational authorities. The clinic was founded in 1934, at the urgent requests

of psychologists and educators that the findings of the Woods Schools relative to dealing with the exceptional child be made available both to the public and to scientific circles.

Mrs. Mollie Woods Hare began her teaching career in the public schools of Philadelphia. It was during this period that she became increasingly impressed with the problem of individual differences in children. She gained her educational experience and insight in her own classroom, as well as in her studies. She became convinced finally that only a school especially planned to train the many types of exceptional children could salvage the latent possibilities of the handicapped child. From this conviction was born the Woods Schools, which, under Mrs. Hare's direction, has expanded to its present national recognition. In 1939 Mrs. Hare was awarded the honorary degree of Doctor of Humane Letters by Temple University, Philadelphia, for her outstanding accomplishments in the field of education.

Abstracts from Current Literature

Physiology and Biochemistry

EFFECT OF CONCUSSION UPON THE POLARIZABILITY OF THE BRAIN. E. A. SPIEGEL, G. C. HENNY, H. T. WYCIS and M. SPIEGEL-ADOLF, *Am. J. Physiol.* **146**:12 (April) 1946.

The polarizability of the cerebrum was studied in cats and guinea pigs after concussive and subconcussive blows produced by a pendulum. Subconcussive blows did not materially alter the polarizability, but severe concussive blows produced a significant decrease. This alteration is a reversible process and indicates an injury to cell membranes. The decrease in polarization is a secondary change, reaching its maximum after the fleeting functional disturbances characteristic of concussion have subsided.

FORSTER, Philadelphia.

EFFECTS OF LOCAL APPLICATIONS OF ACETYLCHOLINE TO THE ACOUSTIC CORTEX. FRANCIS M. FORSTER and ROBERT H. MCCARTER, *J. Neuropath. & Exper. Neurol.* **5**:24 (Jan.) 1946.

The study was initiated to determine the effects of applications of acetylcholine to the auditory receptive area. Fifteen adult cats were studied. Anesthesia was induced with "dial with urethane" in doses of 0.45 to 0.5 cc. per kilogram of body weight. (Each cubic centimeter contains 0.1 Gm. "dial" [diallylmalonylurea], 0.4 Gm. urethane, 0.4 Gm. monoethylurea and water q. s.) The hemispheres were exposed; the dura was reflected, and silver chloride electrodes were used. Recording was by means of a three channel, condenser-coupled ink-writing oscillograph (Grass). Auditory stimuli were administered by clicking a contact key, which was wired in circuit with a signal magnet so arranged as to deflect one writer of the oscillograph. Acetylcholine was applied in concentrations of 5 to 10 per cent and on filter paper pledgets 1 to 2 mm. square. The pledgets were blotted to remove excess acetylcholine.

It was found that the application of acetylcholine to the exposed acoustic cortex of the cat produced a depression of the spontaneous electrical activity of the cortex and of the sound-induced electrical spikes. This was followed by enhancement of the sound-induced spikes, by the appearance of spontaneous acetylcholine-induced discharges and by an after-discharge similar to the spontaneous acetylcholine discharges. Shortly after the appearance of the acetylcholine discharges it was possible to prevent the appearance of these discharges by appropriately timed sound stimuli, so that the cortex was driven in a pattern of augmented auditory spikes and free from acetylcholine discharges. After the acetylcholine discharges had been present for several minutes, usually two to three, it was no longer possible to eliminate the acetylcholine discharges with this procedure.

Distant response to auditory stimulation was also obtained. Spiking discharges in response to auditory stimuli were obtained from a region of the medial suprasylvian gyrus only after the application of acetylcholine to this area resulted in spontaneous acetylcholine discharges. These spiking discharges were synchronous with those obtained in the previously determined acoustic cortex of the upper sylvian gyrus. The spiking discharges of the distant area in response to auditory

stimuli could not be elicited prior to the application of acetylcholine or after the effects of application had disappeared.

Forster and McCarter state that there is a probable correlation between the cortex treated with acetylcholine and the epileptic cortex, and this makes it extremely likely that an area of cortex presenting the pattern of intermittent acetylcholine discharges is undergoing a seizure disturbance.

GUTTMAN, Philadelphia.

REFLEX PUPILLODILATOR MECHANISMS: AN EXPERIMENTAL ANALYSIS. ALBERT KUNTZ and CALVIN A. RICHINS, *J. Neurophysiol.* 9:1 (Jan.) 1946.

Kuntz and Richins studied the reflex pupillodilator mechanisms in cats and dogs. Parasympathetic denervation of the eye was found to produce pronounced enlargement of the pupil, but not to the point of maximum dilatation. Maximal dilation probably requires active contraction of the radial muscle of the iris, which is innervated by sympathetic nerves.

Painful stimuli administered peripherally elicited moderate reflex dilation of the pupil. Sympathetic denervation of the eye did not alter this response, but section of the oculomotor nerve or extirpation of the ciliary ganglion abolished the dilatation. Pupillary dilation due to peripheral painful stimulation is therefore mediated through the parasympathetic nerves. After transection of the lower cervical region of the cord strong stimulation of the hindfoot or of the exposed sciatic nerve produced slight enlargement in animals under pentobarbital anesthesia but no response in nonanesthetized animals. The authors conclude that this observation indicates increased excitability of the ciliospinal center due to the anesthetic agent.

When the pupils have been dilated with atropine, moderate stimulation of the oculomotor nerve produces further dilation. Pupillary dilation following peripheral stimulation is greatly decreased after the intravenous administration of ergotoxine. Kuntz and Richins conclude that these results support the assumption that the pupillodilator reaction mediated through the parasympathetic center of the mesencephalon is actively integrated and controlled and that activation of this center produces inhibition of the circular muscle of the iris.

FORSTER, Philadelphia.

EFFECTS OF INHIBITORS OF CHOLINE ESTERASE ON THE NERVE ACTION POTENTIAL. THEODORE H. BULLOCK, DAVID NACHMANSOHN and MORTIMER A. ROTHENBERG, *J. Neurophysiol.* 9:9 (Jan.) 1946.

Bullock, Nachmansohn and Rothenberg studied the effect of inhibitors of cholinesterase on the action potential of the giant axon and the fin nerve of the squid. Physostigmine alters, and in high concentration abolishes, the action potential of both the giant axon and the fin nerve. The authors point out that this effect is consistent with the concept that acetylcholine is the depolarizing agent released during the passage of the impulse and that the physiologic role of cholinesterase should be the rapid removal of the ester, and that therefore the inhibition of cholinesterase should result in enduring depolarization and abolition of conductivity. The effect of physostigmine is easily reversible. Neostigmine was found to have no effect on the action potential. The difference in the effect of physostigmine and that of neostigmine is explained by the fact that neostigmine is a quaternary ammonium compound and cannot penetrate a lipid membrane, while physostigmine is a tertiary amine and can pass through a lipid membrane. Acetylcholine is also a quaternary ammonium compound and therefore does not alter conductivity when applied externally to the axon but is effective when applied at nerve endings. Bullock, Nachmansohn and Rothenberg conclude that their observations are consistent with the concept that the physicochemical mechanism of conduction along the axon does not differ fundamentally from that in transmission across synapses.

FORSTER, Philadelphia.

THE EFFECT OF CELLULAR HYDRATION ON EXPERIMENTAL ELECTRO-SHOCK CONVULSIONS. EWART A. SWINYARD, JAMES E. P. TOMAN and LOUIS S. GOODMAN, *J. Neurophysiol.* 9:47 (Jan.) 1946.

Swinyard, Toman and Goodman produced cellular hydration in rats by depletion of 40 per cent of extracellular electrolyte without change in the total water content of the body. Under these conditions the threshold of electric shock seizure was lowered by an average of 56 per cent. Cellular hydration of the same degree produced by oral administration of water altered the seizure threshold to an equal degree. When these two methods of cellular hydration were combined, a synergistic effect was observed, and seizures occurred spontaneously. The threshold for metrazol convulsions followed the same alterations as did the threshold for electric shock convulsions. Rapid replacement of electrolytes increased the threshold of electric shock convulsion, and electrolyte given to normal rats raised the normal seizure threshold. An increase in volume of extracellular fluid without alteration of cell volume or concentration of electrolyte does not lower the seizure threshold. The authors conclude that cellular hydration decreases and cellular dehydration increases the seizure level independently of changes in volume of extracellular fluid. Not all antiepileptic drugs raise the normal convulsive threshold. But diphenylhydantoin, phenobarbital and trimethadione ("tridione") significantly raise the threshold of electric shock convulsion lowered by cellular hydration.

FORSTER, Philadelphia.

SYNAPTIC POTENTIALS OF MOTONEURONES. J. C. ECCLES, *J. Neurophysiol.* 9:87 (March) 1946.

Eccles subjected the motoneurons of the cat and frog spinal cords to direct synaptic excitation by a single, synchronous volley of impulses and recorded from the ventral root fibers the resulting potential changes. Blocking of synaptic transmission by deep anesthesia did not interfere with the synaptic potential, a negative change in the motoneuron which was propagated electrotonically along the ventral root fibers. The durations of latent period, rising phase and exponential decay were determined. Synaptic potentials due to two volleys or to repetitive stimuli were summated. Eccles could find no evidence of enduring depolarization, such as occurs in sympathetic ganglia with high frequency stimulation. In unanesthetized animals synaptic potential preceded motoneuron impulses by 0.2 to 0.3 millisecond. Barely blocking the synaptic potential by deepening anesthesia allows the demonstration of facilitation of the response by a second volley administered within fifteen milliseconds. This facilitation is apparently the result of summation of synaptic potentials. The factors governing synaptic transmission would appear to be the synaptic potential acting as a catelectrotonus and the stability of the motoneuron's surface membrane. Blocking of transmission with pentobarbital anesthesia does not affect the time course of the synaptic potential but is effective largely by stabilizing the motoneuron cell membrane and, to a less extent, by diminishing the production of synaptic potential. Synaptic transmission action is of short duration. Curarine was found to have a strychnine-like action on the spinal cord. Physostigmine had no effect on synaptic potentials, and Eccles concludes that acetylcholine plays no important role in synaptic transmission in the spinal cord.

FORSTER, Philadelphia.

THE PYRAMIDAL TRACT: EFFECT OF MAXIMAL INJURY ON ACID PHOSPHATASE CONTENT IN NEURONS OF CATS. WALTER L. HARD and A. M. LASSEK, *J. Neurophysiol.* 9:121 (March) 1946.

Hard and Lassek performed massive cortical removal of the left hemisphere of cats and studied after various survival times the presence or absence of acid phosphatase in both pyramidal tracts. The enzyme was found to disappear from

the axons of the pyramidal tract between the second and third day after cortical removal. The earliest changes were observed in the larger axis-cylinders. During the course of secondary degeneration the enzyme does not reappear. Hard and Lassek conclude that the acid phosphatase technic is a delicate method for determining the integrity and course of degeneration of axis-cylinders following maximal injury to the cells of origin. The presence of the enzyme for a time after destruction of the cells of origin would indicate that the functional activity persists despite the separation of the tissue from the cells of origin. Moreover, in view of the role of phosphatase in phospholipid metabolism, the possibility arises that the axon through its enzyme systems plays an important role in maintaining the integrity of the myelin sheath.

FORSTER, Philadelphia.

A CORTICO-BULBO-RETICULAR PATHWAY FROM AREA 4s. W. S. McCULLOCH, C. GRAF and H. W. MAGOUN, *J. Neurophysiol.* 9:127 (March) 1946.

McCulloch, Graf and Magoun demonstrated by means of the strychnine technic in monkeys a descending connection from the cortical area 4s. This descending pathway diverges from the pyramidal tract in the medulla and apparently ends in the bulbar reticular formation. Since applications of strychnine do not produce strychnine spikes beyond a synapse, the pathway is presumably a direct one. It is not certain whether or not this pathway is myelinated below the pons. Stimulation of area 4s produces relaxation; destruction of this area produces spasticity. The pathway described by McCulloch, Graf and Magoun terminates in a bulbar region, stimulation of which produces relaxation. The authors conclude that the cortico-bulboreticular pathway from area 4s is an extrapyramidal system mediating relaxation.

FORSTER, Philadelphia.

PYRUVIC ACID EXCHANGE OF THE BRAIN. WILLIAMINA HIMWICH and HAROLD E. HIMWICH, *J. Neurophysiol.* 9:133 (March) 1946.

Himwich and Himwich studied the pyruvic acid content of the blood from the internal jugular vein and from an artery in quietly resting, postabsorptive patients. The cerebral venous blood was found to contain small, but significant, increments of pyruvic acid, averaging 0.22 mg. per hundred cubic centimeters. Himwich and Himwich conclude that the brain constantly produces energy without the equivalent utilization of oxygen and that the carbohydrate metabolism of the brain includes not only that portion which is oxidized but also the part split into lactic and pyruvic acids.

FORSTER, Philadelphia.

AN INHIBITORY MECHANISM IN THE BULBAR RETICULAR FORMATION. H. W. MAGOUN and R. RHINES, *J. Neurophysiol.* 9:165 (May) 1946.

Magoun and Rhines observed in cats the blink, flexor and patellar reflexes and the motor responses to stimulation of the motor cortex and the internal capsule. The effects on these movements of bipolar stimulation of the lower portion of the brain stem were observed. The authors found that the bulbar segment of the brain stem contains neural elements capable of exerting an inhibitory influence on a wide variety of motor performances. Motor activity initiated reflexly, by decerebration or by stimulation of the motor cortex, was inhibited. Histologic study of the brain stems revealed that the inhibitory region was distributed in the bulbar reticular formation, especially in the ventromedial portion, and that from this region efferent connections descended to the ventral part of the cord.

FORSTER, Philadelphia.

Neuropathology

MYELOMALACIA OF THE CERVICAL PORTION OF THE SPINAL CORD, PROBABLY THE RESULT OF ROENTGEN THERAPY. LEWIS D. STEVENSON and ROBERT E. ECKHARDT, Arch. Path. 39:109 (Feb.) 1945.

A man received intensive radiation therapy to the cervical region for lympho-epithelioma of the nasopharynx. About two years later signs of transverse myelitis developed in the region of the fourth cervical segment. The myelitis progressed and eventually led to death from respiratory paralysis. At laminectomy the cord appeared normal. Further radiation therapy was without effect on the course of the disease. Postmortem examination revealed myelomalacia of the cervical part of the cord, in the vicinity of which many thickened arterioles with fibrous walls could be seen. This reaction is believed to be an unusual one to roentgen radiation therapy directed to the neck, but one which must be kept in mind when such therapy is contemplated.

WINKELMAN, Philadelphia.

THE BRAIN IN LEUKEMIA. FRANZ LEIDLER and WILLIAM O. RUSSELL, Arch. Path. 40:14 (July) 1945.

A clinical and pathologic study of 20 brains selected at random from persons who died of leukemia was made to determine the type and extent of the pathologic changes occurring in the brain in this disease and to correlate them with the clinical neurologic signs. The gross pathologic study of the brain was carried on as the organ was serially sectioned by means of a slicing machine, the individual slices being not more than from 3 to 5 mm. thick.

In a review of the literature, the authors collected 47 cases of leukemia in which adequate pathologic study of the brain was made; to this group they added the 20 cases on which the aforementioned study was based.

Hemorrhage and infiltration of leukemic cells in the brain, occurring separately or together, were the only significant pathologic changes that could be directly attributed to the leukemic disease. One or both of these pathologic changes were present in 62 of the cases. They were observed in 26 of the 31 cases that could be regarded as selected at random. Grossly visible foci of hemorrhage were present in 46 of the total series of cases and in 19 of the cases in the random series. Infiltrations of leukemic cells in the brain were described in 42 cases, and in 36 of these cases there was hemorrhage in or surrounding the foci of infiltration. Hemorrhage of a proportion to be the immediate cause of death was present in the brain in 27 of all the cases and in 9 of the 31 cases in the random series.

The foci of leukemic cells occurring in the brain in cases of leukemia are similar in all respects to those seen in other somatic tissues in this disease and represent foci of proliferating leukemic cells in the tissue. The infiltrations of leukemic cells in the brain are thought to be an important factor in the production of the hemorrhages in the brain associated with leukemia, since hemorrhage without an accompanying infiltration with leukemic cells was infrequent. Both hemorrhage and infiltrations of leukemic cells in the brain showed a greater predilection for the white than for the gray matter. There does not appear to be any significant difference in the production of lesions in the brain and the development of neurologic signs and symptoms among the various types of leukemia, although hemorrhage and leukemic cell infiltration were slightly more frequent in the chronic than in the acute forms of leukemia.

Neurologic signs and symptoms attributable to the leukemic disease were present in 34 of all the cases included for study but appeared in only 11 of the 31 cases in

the random series. Neurologic symptoms were the first clinical manifestation of the leukemic disease in 5 of the cases. Hemiplegia was observed in 11 cases and was always accompanied with a hemorrhage in the brain of a proportion to be the immediate cause of death. In rare instances neurologic signs and symptoms were exhibited without demonstrable pathologic change in the brain. Signs and symptoms of increased intracranial pressure sufficient to indicate a space-occupying intracranial lesion were only rarely observed, in spite of the fact that in many instances the infiltrations of leukemic cells involved large parts of the brain.

WINKELMAN, Philadelphia.

CORTICAL CEREBELLAR ATROPHY WITHOUT ATAXIA: II. PRIMARY CIRCUMSCRIBED VARIETY. BEN W. LICHTENSTEIN and SAMUEL A. LEVINSON, *J. Neuropath. & Exper. Neurol.* 5:29 (Jan.) 1946.

Lichtenstein and Levinson report 3 cases of atrophy of the cerebellar cortex. The first patient, a Negro, aged 37, was struck on the head with a baseball bat. He became unconscious immediately and was admitted to the hospital within an hour. There was no previous history of disability. The patient was comatose and restless. The scalp was lacerated. Blood was seen in the right external auditory canal, and the mandible appeared deformed. Spinal puncture revealed uniformly bloody cerebrospinal fluid. The patient remained in coma and died twelve days after the accident. Necropsy revealed multiple, sharply circumscribed areas of panatrophy of the cerebellar cortex, characterized by absence of all parenchymatous elements, persistence of the Golgi-Bergmann layer of glia cells and intense gliosis of the degenerated areas. The pons and medulla oblongata were not examined.

The second patient, a Negro woman aged 52, had had pain and weakness in both lower extremities for about six months. For a few weeks she had noted numbness of the legs and weakness of both upper extremities. The only pertinent findings on neurologic examination were tenderness of the lower extremities to pressure, bilateral overactivity of the patellar and achilles reflexes and a positive Babinski sign on the right. Position sense and two point discrimination were lost below the knees.

Study of the blood revealed a hemoglobin concentration of 71 per cent, with 4,800,000 red blood cells. The Kahn reactions of the blood and cerebrospinal fluid were negative. Lumbar puncture revealed normal manometric readings. The cerebrospinal fluid protein measured 90 mg. per hundred cubic centimeters. The patient's clinical course was downhill, despite parenteral injections of liver. The neurologic signs progressed, and the patient had pronounced weakness of both upper extremities, with greatly exaggerated tendon reflexes and a bilateral Hoffmann sign. All sensation was lost below the knees, and urinary and fecal incontinence ensued. Pathologic study revealed multiple, sharply circumscribed areas of atrophy of the cerebellar cortex affecting all the varieties of the parenchymatous elements (parenchymatous panatrophy of the cerebellar cortex, incomplete type) and scattered foci of changes in the nerve cells of the nuclei pontis and the inferior olivary bodies, with atrophy of many of the nerve cells and disappearance of others.

The third patient, a white female infant with an Arnold-Chiari deformity, died at the age of 6 months of hydrocephalus complicating a lumbosacral meningocele. Study of the brain revealed multiple areas of incomplete panatrophy of the cerebellar cortex, characterized by absence of the cells in the external granular layer and of the Purkinje cells and by great diminution of the cells in the granular cell layer.

The study indicates that parenchymatous degeneration of the cerebellar cortex may be a primary disorder, or it may be secondary to degeneration elsewhere in the nervous system. The degeneration may affect only one type of cell exclusively or predominantly, or it may affect all types of parenchymatous elements. Parenchymatous degeneration of the cerebellar cortex is to be looked on as a histopathologic state and not as a disease entity, for it may be observed in a variety of disorders. Sharply circumscribed areas of primary atrophy of the cerebellar cortex characterized by degeneration of the parenchymatous elements and secondary gliosis probably represent the end state of a degenerative process. The pathogenesis is unknown, and many factors, particularly pressure, may play an important role in its causation. The disorder may be asymptomatic and be discovered accidentally at necropsy.

GUTTMAN, Philadelphia.

OLIVOPONTOCEREBELLAR ATROPHY IN A CAT. JOHN W. SCHUT, J. Neuropath. & Exper. Neurol. **5:77** (Jan.) 1946.

An adult cat, killed in an acute experiment, was observed on removal of its brain to possess an abnormally small cerebellum.

The olivopontocerebellar atrophy in this case resembled in incomplete form a similar disorder observed in man. Except for absence of changes in the external arcuate nuclei, the resemblance extended even to such specific characteristics of the human disease as the relative preservation of the vermis and flocculus of the cerebellum, the preservation of the central cerebellar nuclei and the variable involvement of the Purkinje cells. The presence of microscopic changes, such as decrease in the number of Purkinje cells and reduction in the number of nerve cells in the pontile nuclei, permits a differentiation of this case from cerebellar aplasia, hypoplasia or agenesis. True atrophy of the cerebellum in a cat has heretofore not been described.

GUTTMAN, Philadelphia.

SPINAL TRACTS SUBSERVING MICTURITION IN A CASE OF ERB'S SPINAL PARALYSIS. J. McMICHAEL, Brain **68:162**, 1945.

McMichael reports clinical and autopsy studies on a woman aged 47 with urinary retention and weakly extensor plantar responses. Examination of the spinal fluid revealed a slight increase of total protein and a positive Wassermann reaction. Antisiphilic therapy did not alter the clinical picture. The patient died of bilateral infected hydronephrosis and necrotizing cystitis. The pia-arachnoid over the dorsal aspects of the cord was thickened and milky white, and histologic examination revealed perivascular lymphocytic cuffings. Sections of the spinal cord stained for myelin sheaths demonstrated a bilaterally symmetric zone of degeneration anterior to the posterior horns and superficially placed in the lateral columns. McMichael indicates that sensory afferent and motor efferent fibers subserving micturition may pass in the posterior and superficial parts of the lateral columns.

FORSTER, Philadelphia.

Meninges and Blood Vessels

TULAREMIC MENINGITIS: REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH POSTMORTEM OBSERVATIONS. BYRON M. STUART and ROSCOE L. PULLEN, Arch. Int. Med. **76:163** (Sept.) 1945.

Stuart and Pullen report the case of a Negro aged 34 who was admitted to the hospital because of confusion and inability to recognize familiar people and

objects. Five days prior to admission, the patient had a severe shaking chill with profuse sweating. Several hours later, he had a severe headache, which became mild the following day. About thirteen hours prior to admission to the hospital, he felt "dumpy," soon became confused and disoriented and failed to recognize familiar people and objects.

On physical examination the patient was uncooperative, agitated, confused and disoriented and had to be restrained. The temperature was slightly elevated. The pulse rate was 58 per minute and the respiratory rate 20. The pertinent laboratory finding was mild leukocytosis, with a shift to the left. Serologic tests for syphilis gave negative reactions. Lumbar puncture on the day of admission yielded spinal fluid under a pressure of 34 cm. of water. The fluid was turbid and contained 960 white cells per cubic millimeter, with 60 per cent large lymphocytes and 40 per cent small lymphocytes. There was a 4 plus reaction for globulin. The sugar measured 45.4 mg. and the chlorides 643 mg., per hundred cubic centimeters, and the colloidal gold curve was 00012340220. A smear of the spinal fluid showed no organisms. Culture of the spinal fluid yielded no growth in twenty hours. Two days after admission the patient began to spit up frothy and bright red blood. The respiration and pulse were poor; some degree of rigidity of the neck was noted, and examination of the chest still revealed nothing abnormal. On the third day after admission the patient had two generalized seizures. He was treated with sulfa-pyridine, administered intravenously. He died six days after admission to the hospital.

Gross examination of the brain at necropsy revealed clear spinal fluid. The subarachnoid vessels were greatly dilated. There were a few patches of grayish white exudate in both hemispheres, particularly in the frontal regions. These were limited to the sulci. Microscopic examination of the brain revealed a few small and large round mononuclear cells, of inflammatory character, in most sections of the meninges. All sections of the cortex showed extreme congestion and severe degeneration of ganglion cells, the latter being greatly out of proportion to the degree of inflammation. Disappearance of ganglion cells was also noted in the basal ganglia and in the brain stem. There was an abundance of yellow, pigmented granules, some of which were free and some within the large mononuclear cells. The infiltration was severest in the choroid plexus. The ependyma of the lateral ventricles showed plaque formation and subependymal gliosis. In the medulla there were several subependymal petechiae.

Culture of the lungs revealed streptococci. Guinea pigs inoculated with substance from the lungs and the brain became ill and were studied at autopsy on the fourth day. Each showed numerous miliary lesions in the spleen consistent with the diagnosis of tularemia.

The authors state that tularemia should be considered in the diagnosis of obscure forms of meningitis and, in turn, evidence of meningeal involvement should be sought for in gravely ill patients with tularemia. To date, no patient with tularemic meningitis has recovered. There are now, in all, 6 reported cases in the literature. It is stated that therapy is of no avail, although one should use all available chemotherapeutic agents, including penicillin, the sulfonamide compounds and Foshay's antiserum.

GUTTMAN, Philadelphia.

NEUROLOGIC COMPLICATIONS DURING MENINGOCOCCIC MENINGITIS TREATED WITH SULFONAMIDE DRUGS. THOMAS W. FARMER, *Arch. Int. Med.* 76:201 (Oct.) 1945.

The purpose of this paper is to outline the clinical course and prognosis in a variety of neurologic complications of meningococcic meningitis. The data were

obtained from a study of approximately 300 patients with meningococcic meningitis during the years 1942, 1943 and 1944. About 100 of the patients were children. Of the 300 patients, focal neurologic complications were observed to develop in 26 during the course of meningococcic infections. In each of these patients it was ascertained that the paralysis did not exist before the onset of the meningeal infection, and that no other neurologic disease was concomitant with the meningitis.

The etiologic diagnosis was established for 24 of the 26 patients by the isolation of meningococci, group I, from the cerebrospinal fluid. For the remaining 2 patients, presumptive diagnoses were based on the observations of meningeal signs, a petechial cutaneous eruption and purulent cerebrospinal fluid. All 26 patients received sulfonamide therapy: Sixteen received sulfadiazine; 7 were treated with sulfamerazine; 2 received sulfapyrazine, and 1 was treated with sulfathiazole. All the patients recovered.

The 26 patients with focal neurologic abnormalities were carefully followed for three years. Among them were 9 patients with paralysis of the sixth nerve, 9 with paralysis of the seventh nerve, 5 with paralysis of the eighth nerve and 3 with transient focal cerebral complications.

Paralyses of the cranial nerves present characteristic clinical features. Paralysis of the sixth nerve, the most common palsy of the extraocular nerves, usually develops early in the course of meningitis, when the cerebrospinal fluid is purulent. It is usually unilateral, and complete recovery within a few weeks is the rule. Unilateral and bilateral paralyses of the seventh nerve are usually late complications, which develop after the cerebrospinal fluid has become clear. In 4 patients with facial diplegia late onset of paralysis during convalescence was characteristic. Recovery of function usually requires several months. It is complete in most, but not in all, cases. Paralysis of the eighth nerve with deafness is the most serious complication of the cranial nerves. It occurs more commonly among children than among adults and is usually bilateral. Its present incidence is approximately 5 per cent. It may develop during the acute meningitic infection, during convalescence or even after recovery. Deafness is permanent in the vast majority of cases. In young children deaf-mutism results. Occasional cases of transitory deafness also occur.

Cerebral complications with convulsions and transient hemiplegia occur rarely. They usually appear late in the course of the infection, with clear cerebrospinal fluid. The convulsions may be unilateral or generalized. They are followed by hemiparesis with occasional aphasic disorders and hemianopsia. Electroencephalograms reveal focal disturbances in the area involved. All these neurologic and electroencephalographic signs were observed to clear completely, with no residual signs.

GUTTMAN, Philadelphia.

ADRENAL HEMORRHAGES IN MENINGOCOCCIC SEPSIS. J. SCHWARZ, *Arch. Path.* 41:503 (May) 1946.

A fulminant type of sepsis, with purpura and cyanosis of the skin and adrenal hemorrhages, frequently occurring in the presence of a thymolympathic constitution, especially in children, and generally caused by *Neisseria meningitidis* (*Neisseria intracellularis*), is wrongly given the name "Waterhouse-Friderichsen syndrome." Neither Waterhouse nor Friderichsen, but Voelcker, in 1894, was the first to describe this syndrome. Waterhouse, in 1911, and Friderichsen, in 1918, published studies, the merit of which does not justify the use of the name "Waterhouse-Friderichsen syndrome," suggested by Thomas and later by Glanzmann and others.

A descriptive term, such as "fulminant sepsis with adrenal hemorrhage" or "meningococcic adrenal syndrome" is more appropriate and less erroneous than the present name.

The intracranial anatomic lesions have been described as varying from "none" to the presence of purulent meningitis or encephalitis, but in several cases in which macroscopically there were no lesions meningitis was demonstrated microscopically; therefore, in cases in which clinically there are no meningeal signs and in which macroscopic inspection of the leptomeninx does not appear to show anything abnormal there may be definitive inflammation of this membrane.

In the cases observed, inflammatory lesions were not seen in the adrenal glands, nor was thrombosis of the adrenal veins observed. Definite hyperplasia of the thymus and hypoplasia of the adrenal glands occurred.

WINKELMAN, Philadelphia.

TREATMENT OF CHRONIC INFLUENZAL MENINGITIS: HEPARIN AS ADJUVANT.
E. S. PLATOU, R. W. GIBBS and F. H. ADAMS, *Journal-Lancet* 66:157 (May) 1946.

Platou and his associates show that heparin given intrathecally in the acute stages of infantile meningitis is worthy of trial to avert chronicity, with its potentially serious or fatal sequelae. In chronic meningitis due to *Hemophilus influenza* the problems of exudate in the small avenues of communication of the foramina and the subdural spaces, lack of adequate concentration of antibody in these areas and insufficiency of bacteriostasis may arise singly or in combination. Poor drainage, disparity in the character of fluid from the ventricle and the spinal canal, abnormally high protein levels and persistently low sugar levels are suggestive adjuncts to diagnosis in the presence of clinical signs of rigidity, tremor, opisthotonos and growth of the organism in cultures of the cerebrospinal fluid. Intrathecal serum may furnish the desired concentration but may also enhance the problem because of local antibody-antigen reaction. Heparin may help liquefy exudate, and air injected later may open the delicate pathways so that curative mediums may reach their goal. Recent studies suggest that streptomycin may complement, or even supplant, sulfonamide compounds as a bacteriostatic agent against *H. influenzae*. The 3 cases reported meet the criteria of chronic influenzal meningitis. Intrathecal and intraventricular therapy was carried out with antibody. Heparin, air and injection of complement, as well as specific therapy, as suggested by Alexander, were used. The treatment was successful.

J. A. M. A.

TREATMENT OF PNEUMOCOCCIC AND STAPHYLOCOCCIC MENINGITIS WITH PENICILLIN AND SULFONAMIDES: REPORT OF 20 CASES. W. H. HALL, J. ALDEN, G. M. BURT and W. W. SPINK, *Minnesota Med.* 29:553 (June) 1946.

Of 17 patients with pneumococcic meningitis whom Hall and his associates treated with penicillin, 13 recovered. Sixteen of the 17 patients received sulfadiazine or sulfamerazine in addition to the penicillin. Of 3 infants with staphylococcic meningitis who were treated with a combination of penicillin and sulfonamide drugs, 2 recovered. The authors recommend that in the treatment of suppurative meningitis due to pneumococci or staphylococci penicillin be administered intravenously or intramuscularly and intrathecally. In addition, sulfadiazine or sulfamerazine should be given orally or parenterally, but not intrathecally. The importance of early diagnosis, supportive treatment and eradication of suppurative foci is stressed.

J. A. M. A.

Diseases of the Brain

ASPHYXIA OF NEWBORN INFANTS. J. D. RUSS and R. A. STRONG, *Am. J. Obst. & Gynec.* **51**:643 (May) 1946.

Russ and Strong studied 1,048 cases of asphyxia in newborn babies. Mild asphyxia occurred in 471 cases, with 3 deaths; moderate asphyxia occurred in 420 cases, with 14 deaths, and severe asphyxia occurred in 157 cases, with 52 deaths. Anoxemia, from many causes, is responsible for 18.5 per cent of all deaths in newborn babies. Among the most frequent contributing factors of anoxemia are the age and parity of the mother, duration of labor, type of delivery, prepartal analgesia and the anesthetics used during delivery. Less frequently, prematurity, premature separation of the placenta, bleeding placenta previa or short cord may cause anoxemia. Anoxemia prolonged more than two minutes after delivery will cause serious cerebral changes. Prompt initiation and maintenance of respiration within thirty seconds after cutting the cord will prevent these changes, and if respiration is established before two minutes it may oxygenate the blood sufficiently to arrest any changes which have begun. Actual aspiration with the use of an intratracheal catheter and subsequent insufflation of the lungs constitute the truly reviving technic. The after-care of the newborn resuscitated baby is of equal importance with the resuscitation itself.

J. A. M. A.

PLEURAL SHOCK AND CEREBRAL EMBOLISM. J. B. ANDOSCA and J. A. FOLEY, *Am. Rev. Tuberc.* **52**:221 (Sept.) 1945.

According to Andosca and Foley, pleural puncture, employed in pneumothorax therapy, in aspiration of an empyema cavity or in exploratory thoracocentesis, may result in signs and symptoms which have been diagnosed as pleural shock or as cerebral embolism. The confusion which exists between the two diagnoses gives a false impression concerning the seriousness of the complication. Pleural shock is rare and may occur in excitable and neurotic patients, but the symptom complex of cyanosis, changes in respiration and circulation, convulsions, ocular disturbances, loss of consciousness, aphasia, paralysis and sometimes death occurring during pleural puncture is definitely due to cerebral embolism. The treatment consists in lowering the patient's head and giving cardiac stimulants. The prognosis in a case of cerebral embolism depends on the amount of air entering the blood stream and the region of the brain most seriously involved. The authors have encountered 12 cases, with 3 fatalities, in a series of 90,120 pleural punctures at the Boston Sanatorium. One of the fatal cases was attributed to procaine hydrochloride poisoning. Procaine hydrochloride in a 1 per cent solution should be employed only for the initial pneumothorax treatment, and not for the subsequent refills.

J. A. M. A.

CRANIOTOMY AND TOTAL DISSECTION AS METHOD IN TREATMENT OF ABSCESS OF THE BRAIN. E. F. FINCHER, *Ann. Surg.* **123**:789 (May) 1946.

According to Fincher, results as seen in the literature on cerebral abscess which have been removed in toto have been surgically ideal. These wounds have healed by primary intention, and the patients have escaped the prolonged complications of hospitalization, and often fatal results, that have followed other methods of treatment. In the author's 5 cases radical total dissection was carried out, aided by sulfonamide and penicillin therapy; and the period of hospitalization has been comparable to that of a normal convalescence period for any craniotomy. The

morbidity, with 1 exception, has been nil. The results thus far have been such as to suggest that the basic surgical principle of "incision and drainage" in the treatment of abscesses of the brain might be replaced by total dissection of the abscess and primary closure of the wound.

J. A. M. A.

CHANGES IN THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH ENCEPHALITIS COMPLICATING PNEUMONIA: I. A CLINICAL STUDY. A. B. BAKER and H. H. NORAN, *Arch. Int. Med.* **76**:146 (Sept.) 1945.

Baker and Noran report the histories of 6 patients who had some form of encephalitis associated with pneumonia. Two of the patients were infants; 1 was a 10 year old girl, and the remaining 3 were adults. The authors believe that, in view of the type of cerebral complications which take place, the organism which is responsible for the pneumonia probably does not produce the encephalitis. They therefore limit the etiologic field to three considerations: (1) the toxic theory, (2) the virus theory and (3) the allergic theory.

The observations presented indicate that, regardless of the causative organism, complications of the central nervous system may follow pneumonia. The severity of the encephalitis does not correlate with the severity of the pulmonary involvement. In other words, relatively mild pneumonia may be followed by severe cerebral damage.

Clinical pictures produced by involvement of the central nervous system can be divided into five types, each showing definite clinical characteristics which may be of both diagnostic and prognostic significance: (1) the type characterized by generalized symptoms of a nonspecific nature (headache, vomiting, lethargy and irritability), (2) the delirious type, (3) the convulsive type, (4) the lethargic type and (5) the hemiplegic type.

GUTTMAN, Philadelphia.

CAUSE, EFFECT AND TREATMENT OF AIR BLAST INJURIES. R. E. TUNBRIDGE, *War Med.* **7**:3 (Jan.) 1945.

Injuries due to air blast are best divided into three types: mild, moderate and severe.

The mild injuries are readily overlooked. The symptoms are not severe—tightness of the chest, pain under the sternum or in the chest, irritable and paroxysmal cough or slight deafness; in fact, they may appear to be so out of keeping with the general well-being of the patient as to lead to their being considered psychosomatic manifestations. Treatment consists of rest, mild sedation and reassurance. Recovery is complete within fourteen days.

The moderate injuries are frequently accompanied with other injuries, and the visual evidence of wounds often leads to the overlooking of injuries due to air blast. Associated surgical conditions should be treated on their merits, and operation or blood transfusion should not be withheld on account of the presence of blast injuries. The prognosis of severe wounds associated with blast injury is worse than that of wounds not so complicated, but treatment, namely, rest and administration of oxygen, is not affected.

The severe injuries present no problem because the patient rapidly loses consciousness and usually dies within twelve hours. Temporary relief is sometimes afforded by venesection, but morphine is the chief therapeutic weapon.

The sequelae from air blast are few: deafness and postconcussive syndromes. The pulmonary lesions in persons with nonfatal injury, unless secondarily infected, resolve completely.

PEARSON, Philadelphia.

DISSOCIATED PARALYSIS OF THIRD NERVE DUE TO A MENINGIOMA EN PLAQUE OF THE LESSER WING OF THE SPHENOID BONE, REVEALED BY ROUTINE ROENTGENOGRAPHIC EXAMINATION OF THE SKULL. R. GARCIN, M. KIPFER, M. ROSIER and H. X. MAN, *Rev. neurol.* **77**:153 (May-June) 1945.

A man aged 20 was seen on March 25, 1944 because of paralysis of the right third nerve of six months' duration. All the external muscles of the right eye supplied by the third nerve were involved and there was mild ptosis. There was no internal ophthalmoplegia. This dissociation of involvement of the internal and the external musculature of the eye at first suggested a central lesion, perhaps a virus infection. There was no syphilis or diabetes. Routine roentgenograms of the skull showed abnormal density of the lesser wing of the right sphenoid bone and narrowing of the right sphenoidal fissure. Mild headache in the right frontal area appeared in November 1944. An operation was performed on December 13. A meningioma *en plaque* was observed in the region of the lesser wing of the right sphenoid bone. The dissociated nerve paralysis persisted after the operation.

N. SAVITSKY, New York.

PEARLY TUMOR OF THE CEREBELLOPONTILE ANGLE. T. ALAJOUANINE and R. THUREL, *Rev. neurol.* **77**:196 (July-Aug.) 1945.

Alajouanine and Thurel report an unusual case of pearly tumor of the cerebellopontile angle, with successful operation. The sudden onset with peripheral facial palsy was unusual, the palsy being the only symptom for ten years. The patient, a man aged 44, had sudden onset of palsy of the left side of the face, of peripheral type, at the age of 30; this persisted for fourteen years, with no sign of improvement. Ten years after the onset, tinnitus and loss of hearing appeared on the left side. Deafness was complete in the left ear three years afterward. Attacks of dizziness began to recur eleven years after the onset; two years later difficulty with equilibrium became worse. Almost fourteen years after the onset, the clinical findings were complete palsy of the left side of the face, peripheral in type; mild involvement of the left trigeminal nerve; abolition of the left corneal reflex, and fibrillations in the left masseter muscle. There were complete deafness on the left side with absence of caloric responses, spontaneous horizontal nystagmus toward the right, outward past pointing on the left, a tendency to veer backward and to the right in the Romberg position and signs of cerebellar involvement on the left. The fundi were normal. Operation revealed a rather large pearly tumor in the left cerebellopontile angle. There was no trace of the left facial nerve, and the left eighth nerve appeared very thin. The patient's condition improved after the operation, despite transitory dysphagia, and he was able to return to work. The dizziness and nystagmus disappeared; the deafness improved somewhat. The paralysis of the face remained unchanged.

N. SAVITSKY, New York.

Peripheral and Cranial Nerves

ACUTE INFECTIOUS POLYNEURITIS (GUILLAIN-BARRÉ TYPE). JOSEPH G. CHUSID and GILBERT H. MARQUARDT, *Ann. Int. Med.* **23**:852 (Nov.) 1945.

Chusid and Marquardt report the case histories of 6 patients who became ill with acute infectious polyneuritis while they were in India. At one time or another all these patients had symptoms which included paresthesias, dysesthesias and various types of paresis. Neurologic signs included palsies, pareses and sensory disturbances of the cranial nerves. Four of the patients had gastrointestinal symptoms and diarrhea during some stage of their illness. In several of the cases the

first diagnosis was acute anterior poliomyelitis. The authors state that the differentiation between so-called acute infectious polyneuritis of the Guillain-Barré-Strohl type and acute anterior poliomyelitis can be made chiefly on the finding of albuminocytologic dissociation of the cerebrospinal fluid with the former.

GUTTMAN, Philadelphia.

FACIAL PARALYSIS IN ACUTE OTITIS MEDIA AND USE OF PENICILLIN. EDWARD M. GLASSBURN, Arch. Otolaryng. **41**:218 (March) 1945.

Facial paralysis occurring during the course of acute otitis media is a rare and alarming development. It occurs approximately once in every 200 cases. Possible causes advanced for the paralysis are: (1) infection of the nerve by contact, (2) compression of the nerve by hyperemic blood vessels which accompany the nerve, (3) lymphangitis in the facial nerve canal and (4) toxic paresis of the vasomotor nerves and consequent disturbances in the nutrition of the nerve.

In the last few years, the literature on the occurrence of facial paralysis early in the course of acute otitis media stresses conservative, nonoperative treatment. Prior to the advent of the sulfonamide drugs, mastoidectomy was advocated on an emergency basis, regardless of the time of onset of the paralysis. Introduction of the sulfonamide drugs, together with the more recent advent of penicillin, has led to a critical analysis and revision of surgical indications in cases of acute otitis media and mastoid disease. That the appearance of facial paralysis in cases of this type will be regarded as a medical, and not a surgical, problem is strongly suggested by the efficacy of penicillin in the treatment of acute otitis media.

Glassburn reports 3 cases of facial palsy which occurred during the course of acute otitis media. Under a conservative medical regimen, the progress was satisfactory. Two patients received penicillin in addition to sulfonamide therapy, while 1 received only sulfadiazine. The return of function for hearing and facial motion was complete in all cases. The author believes that the recovery from facial paralysis is dependent on immediate control of the otitis and that the trend toward conservative treatment of otitic facial palsies will be advanced by the results of penicillin therapy.

RYAN, Philadelphia.

VERTIGO IN HYPOTHYROIDISM. A. G. ATHENS, Minnesota Med. **29**:562 (June) 1946.

Athens reviews observations on 30 patients who had recurring attacks of vertigo, fatigue, a low basal metabolism and low blood pressure. Desiccated thyroid generally gave relief from symptoms in the 25 patients who were treated. There is a similarity between this symptom complex and Ménière's syndrome. The author suggests the possibility of attacks of vertigo being precipitated by the accumulation of waste metabolic products in the endolymph and advises that routine basal metabolic studies and determinations of the blood cholesterol be made in patients with Ménière's symptom complex.

J. A. M. A.

COCHLEAR DEAFNESS. A. J. WRIGHT, Proc. Roy. Soc. Med. **39**:265 (March) 1946.

Many otologists consider that Ménière's disease is an entity and that the auditory disturbances, in the form of deafness and/or tinnitus, precedes the vertigo in the majority of cases, often by a long period. The present paper endeavors to draw a more detailed picture of the disease as seen in the absence of vertigo.

Most commonly occurring in an adult, of either sex, the disease is occasionally observed in children. The earliest symptom is usually tinnitus, with a variable period elapsing before any appreciable deafness is observed. Occasionally (in 7 per cent of cases) a dramatically sudden onset is reported. Trauma is frequently given as the exciting cause, including everything from an explosion to a cold draft of air. Again, paracusis may be the original symptom, or hyperacusis, the latter being frequently accompanied with tinnitus. The amount of hearing loss varies; subjectively it is usually reported as unilateral, although careful measurements reveal bilateral involvement. In 8 per cent of the author's cases there was high grade deafness in both ears, and the deafness was usually definitely bilateral at the onset. The type of hearing loss is perceptive, although care must be taken in interpretation, as often a mistaken diagnosis of conduction deafness is made with the tuning fork tests. The earliest loss is usually for high tones; later all tones are involved. There is, however, no typical audiogram for Ménière's disease. Masking of the good ear in the Rinne test is essential, especially in cases of pronounced unilateral deafness. Weber's test does not so frequently lead to error.

A frequent, and often early, symptom is paracusis, which may persist to a late stage. It is described as a general distortion and jangling of sounds, but a musical ear may perceive notes as sharp or flat; in 6 cases in the author's series the high tones were sharp, the low tones flat. The presence of variability in hearing is almost diagnostic, and tinnitus often follows the same course. Sensory phenomena, ranging from a sense of fullness to actual pain and headache, are noted in the majority of cases. The complaint of unpleasantness, or even pain, associated with loud noises may be found in the early or late stage of the disease. Often the earliest symptom, and the most constant, is tinnitus, which was found to be absent in only 4 per cent of the author's cases.

In 20 per cent of the author's cases there were old changes in the tympanic membrane or the middle ear, consisting of scarring, opacity or retraction. On several occasions, in addition to gross disease, a dilated vessel down the handle of the malleolus or, rarely, a hyperemic blush on the inner tympanic wall was seen.

BERRY, Philadelphia.

VESTIBULAR INJURIES. T. CAWTHORNE, *Proc. Roy. Soc. Med.* **39**:270 (March) 1946.

In a study based on the comparison of 120 cases of deliberate destructive operations on the labyrinth for the relief of Ménière's disease and 58 cases of closed head injury with labyrinthine signs, Cawthorne concludes that in cases of persistent vertigo following concussion the vestibular end organ is the likely seat of damage. The clinical picture is complicated by psychologic disturbances, often sufficient to divert attention from the underlying cause, but explanation of the true nature of the state of affairs and a series of graduated exercises encouraging movements of the head and eyes form the most satisfactory basis for hastening recovery. If this regimen of treatment is begun soon after operation, return to useful occupation is expected within a month, and chronic invalidism need not result from head injuries.

Although pathologic proof is lacking, postconcussion vertigo is assumed to be due to damage of the end organ in the labyrinth because of similar clinical signs and symptoms in the two conditions. In nearly all the observed cases of prolonged vertigo the condition was the result of "acceleration concussion," in which the head was freely movable at the time of injury. The author explains by analogy: In the cochlea exposure to loud sounds may result in a disturbance of the endolymph sufficient to cause permanent damage to the organ of Corti. Both cochlear and vestibular end organs rely for essential stimulus on displacement or deformation by movement of the endolymph, and it is reasonable to suppose that if one end organ suffers actual damage from overstimulation, the other may suffer in a like manner. "The facts that vertigo is the cardinal symptom in a damaged labyrinth, and that a frequent sequel of concussion is vertigo support this hypothesis."

The author describes clinically what he terms the syndrome of "acute vestibular failure": overwhelming vertigo, "awful sickness" and turbulent movements of the eyes, all increased on movement of the head. This syndrome is seen when a previously functioning labyrinth is completely and suddenly overwhelmed, whether by operative procedures of labyrinthotomy or labyrinthectomy or by head injury. The intensity varies from case to case and may be masked by the effect of injuries elsewhere. The acute phase subsides within a few days, leaving a residual vertigo consisting of a sensation of apparent movement, either objective or subjective, typically induced by sudden alteration in posture or turning of the head. Other residual symptoms include a sensation of slight movement of the ground, like the roll of a ship; inability to focus the gaze on an object for any length of time and the dislike of looking at rapidly moving objects; instability in the dark and on climbing and descending stairs or an inclined plane, and a tendency to tire quickly on physical exertion. Headache, though common in cases of concussion, is infrequently observed after labyrinthine operations and is discarded as part of the vestibular disorder.

Of the 58 cases of head injury, deviation from the normal in response to caloric stimulation was present in 56, and in 1 of the remaining cases vertigo had disappeared several days prior to the caloric test. Of the 56 cases, damage to the cochlea was present in only 24.

In discussing Cawthorne's thesis, Mr. E. D. D. Davis commented on 57 cases of injury to the ear resulting from fractured skull in his experience; in only 5 of these was there demonstrated damage to the internal ear, which in all but 1 case was limited to the cochlea. Labyrinthine damage was found in 1 case. He postulates cerebral concussion or damage as the cause of vertigo following head injuries.

BERRY, Philadelphia.

PARALYSIS OF THE RADIAL NERVE DUE TO SERUM THERAPY (PATHOGENIC ROLE OF URTICARIA). T. ALAJOUANINE, R. THUREL and R. TRICOT, *Rev. neurol.* 77:130 (May-June) 1945.

A man aged 44 sustained an injury to the left index finger on Nov. 22, 1944. Two days later 10 cc. of tetanus antiserum was injected into the right thigh. On November 30 serum sickness with generalized urticaria appeared; this cleared up in forty-eight hours. On December 2 he began to complain of pain in the neck and the upper limbs. After sleeping flat on his back for two or three hours, he awoke with a left wrist drop. The pain had become less severe and was localized to the paralyzed limb. All muscles supplied by the radial nerve except the triceps were involved. There was some diminution of sensation in the dorsal aspect of the first interosseous space. The completeness of involvement with sensory and motor components of the nerve favored the explanation that urticarial swelling exerted a mechanical effect on the nerve fibers. The authors emphasize that involvement of periscapular muscles is not pathognomonic of serum paralysis.

N. SAVITSKY, New York.

Book Reviews

Are You Considering Psychoanalysis? By Felix Ocko, M.D. Edited by Karen Horney, M.D. Price, \$3. New York: W. W. Norton & Company, Inc., 1946.

This book is written for popular use. There has been a great increase in interest on the part of the laity in psychology, psychiatry and psychoanalysis. To many people psychiatry and psychoanalysis are synonymous, so that persons who have had one or two meetings with a psychiatrist of any school of thought believe that they are being "analyzed," and that every psychiatrist is automatically a psychoanalyst. For such persons this book will be truly informative.

Most educated Americans have heard of Freud and read some of his writings with more or less understanding. One of the well known writers on analytic subjects in America has been Dr. Karen Horney, whose books have had a wide circulation. Originally a member of the orthodox freudian school of psychoanalysis, Dr. Horney has enlarged on and revised certain of Freud's formulations to the extent that she has become the founder of a new school of psychoanalysis, utilizing the basic contributions of Freud. When the Association for the Advancement of Psychoanalysis was founded in 1941, the program on community education in psychoanalysis included a series of lectures for the laity, given by recognized analysts, all of whom are affiliated with the association. This book is the outgrowth of one of the series of lectures. As editor, Dr. Horney has given the book unity. The authors include Drs. Horney, A. R. Martin, Valer Barbu, Muriel Ivimey, Harold Kelman and Elizabeth Kilpatrick. As in all books associated with Dr. Horney, the fluidity and lucidity of the presentation are especially commendable.

An attempt is made to answer and expound the many questions asked by the person considering psychoanalysis. "What is a neurosis?" "Why psychoanalysis?" "What Do You Do in Analysis?" "What Does the Analyst Do?" "How Does Analysis Help?" and "How Do You Progress After Analysis?" are the titles of some of the chapters. The basic concepts of all schools of psychoanalysis are explained in nontechnical language, together with the differences and emphases of the several derivative groups. This is given in a cursory manner. Emphasis is placed on the Horney viewpoint that psychoanalysis is equally concerned with "what goes on between individuals" and "disturbances inside the individual." The focus is "on the individual in his human environment or social setting in its broad sense."

The psychoanalytic credo of the Horney school is stated so succinctly as to bear quotation: "We believe that man is constructive by nature and becomes destructive only when his genuine urge to grow and develop has been frustrated. It is upon these latent constructive forces in the patient and his environment that we count so heavily to help him out of his difficulties. We believe that man by his own efforts can free himself of the consequences of those inimical forces which made him destructive. We believe that within the limitations of his natural endowment and those imposed and created by his parents, his culture and his physical environment, man can exercise a choice regarding the ways and directions of his self-betterment. We believe that people can live together in a truly democratic society and in a spirit of mutuality even though for the present, and for some time to come, the strongest stimuli driving them toward that goal may be a survival need and a fear of the consequences of the monstrous destructiveness created and unloosed."

Psychoanalysis is a growing experience for the patient. During analysis the patient will "visualize goals and work toward their attainment. These goals are—becoming acquainted with yourself as you are (not as you think you are); understanding your particular conscious and unconscious attempts at solutions of problems which confront you; evaluating these solutions and their effects on your life;

changing conditions in your personality by resolving neurotic conflicts, and when your real self has become free, mobilizing your resources in directions of your own choosing."

The profound change in personality structure of the patient which is the goal of the analysis should indicate to the prospective patient that analysis is more than just a confession or a mother-child teaching relationship, in which specified rules for untroubled living are dispensed. The patient must work out the various bases for his neurotic trends, working through the resistances his unconscious presents. The technique of this is briefly explained. The patient may feel humiliated, angry, frightened and anxious as he begins to learn more truths about himself and is faced with the need of doing something about them. The relationship with the analyst is an intense one, never a passive experience. The analysis may be a tremendous task for the patient. But it is a cooperative enterprise. The analyst endeavors to find out together with the patient in what manner he is blocking his own way. His main task is to help the patient live "under his own jurisdiction," recognize his own wishes and find his own set of values. Through his interpretations, explanations and questions, the analyst influences the course of the analysis, the final goal being a whole and well integrated personality.

A final chapter of unusual interest is called "How Do You Progress After Analysis?" It emphasizes that analysis is not a definitive procedure in the sense that all patients who have completed an analysis emerge from the process as completely integrated, secure individuals who will never have any further problems. Analysis is not an absolute attainment. As Dr. Horney states: "It is an endless road toward a destination it never reaches." But it does make the analysant aware of his true goals, and guides and prevents him from aimlessly stumbling through life by giving him inner strength and freedom.

The more practical aspects to a patient considering analysis—Who should my analyst be? How long will it take? How much will it cost?—are discussed briefly in an early chapter.

While the book is definitely directed toward the person who is already considering analysis as a means to help himself, or is at least aware of his need for psychiatric help, and as such performs an essential function in an admirable manner, it is to be regretted that nowhere within its covers is there any discussion of the applicability of psychoanalysis or of some of its basic tenets to the better functioning society as a whole.

A Textbook of Clinical Neurology. By J. M. Nielsen. Second edition. Price, \$7.50. Pp. 699, with 190 illustrations. New York: Paul B. Hoeber, Inc., 1946.

The personal flavor given to a textbook is usually to be found in the preface and in the last few words before the index. This is abundantly true in the new edition of this excellent volume. Nielsen himself is little short of a walking encyclopedia of neurology, and has probably gone farther than anybody else living in familiarizing himself with the landmarks in clinical neurology. These he lists with the observation, "They have been gathered here as fundamental works with which all students should be acquainted."

Yet Nielsen's work is not in any sense encyclopedic. It is far from a recitation of dull facts that have been handed down from textbook to textbook together with the accumulation of the barnacles of error that are so often perpetuated. Every page bears the imprint of his own thinking and experience, and these have been both wide and profound. The case reports and illustrations are fresh and are taken from that museum of living pathology which is the Los Angeles County Hospital, supplemented by specimens studied at the Cajal Laboratory of Neuro-pathology, directed by Courville.

Nielsen is at his best in the field of clinical cerebral localization, and his chapters on aphasia, apraxia and agnosia are masterly in their practical delineation of this particularly difficult field. He has revised the sections on electroencephalography, sulfonamide compounds and penicillin in order to present the current understanding of these diagnostic and therapeutic methods. His "organic"

orientation causes him to take a sly dig or two at "certain faiths which teach that all disease is due to erroneous thoughts," and he wisely limits the discussion of disorders of the vegetative nervous system to the physiologic aspects rather than include the whole subject of psychosomatic medicine. The student, he believes, can gain the necessary orientation in this field from recent psychiatric texts. Nevertheless, the section on the psychoneuroses serves to round out the presentation of clinical neurology as given in the rest of the volume.

Nielsen's book is a large one, crammed with facts, but, fortunately, these facts are presented in such a way that the students will be able to harmonize them and thereby gain a much better grasp of the whole field of clinical neurology.

Their Mothers' Sons: The Psychiatrist Examines an American Problem.

By Edward A. Strecker, M.D. Price, \$2.75. Pp. 220. Philadelphia: J. B. Lippincott Co., 1946.

This book is a warning to mothers of the United States to liberate their sons and thus make for less neurosis in American society. The reader will find in this volume an excellent description of the different forms and expressions of "mother love" and the subtle means that "Mom" uses to keep her son from becoming a mature man. Strecker stresses the responsibility of the sincere mother slowly, intelligently and kindly to wean her son from herself and so develop in him the independent strength of maturity. The volume is recommended.

The Anatomy of the Nervous System: Its Development and Function.

By Stephen Walter Ranson, M.D., Ph.D., Late Professor of Neurology and Director of Neurological Institute, Northwestern University Medical School, Chicago. Revised by Sam Lillard Clark, M.D., Ph.D., Professor of Anatomy, the Vanderbilt University School of Medicine, Nashville, Tenn. Eighth edition. Price \$5. Pp. 532, with 417 illustrations, 14 in color. Philadelphia: W. B. Saunders Company, 1947.

The new generation of medical students will be happily introduced to their neuroanatomy, not through the dark green-covered "Ranson," so familiar to and prized by their predecessors since 1920, but to the new, brown-covered Ranson-Clark edition, which will likewise long merit the approbation of their successors. Thus have the publishers marked the designation of Dr. Clark by Dr. Ranson himself as his successor.

The co-author has well fulfilled Dr. Ranson's hopes. The eighth edition emerges as an up to the minute, basic book, for cognizance has been taken of all facts gleaned from recent studies on man, monkeys, cats, rabbits, dogs and chicks. The addition of some fifty new worldwide contributions to the bibliography of five hundred odd references attests the thoroughness of the revision. Thus the researches have amplified and clarified some aspects of knowledge of the cerebral cortex, cerebellum, choroid plexus and trigeminal pathways; the cochlear, vestibular and optic nerves, and the thalamic nuclei, and these sections have been rewritten.

The presentation of material has been altered for easier use by consolidating all gross descriptive anatomy into one opening section. Most of the original, incomparable, illustrations have been retained, and an excellent new series of nine parasagittal sections of the human brain stem has been added.

The book is highly recommended as achieving its purpose of presenting the developmental and functional significance of structure of the nervous system and its correlation with the interpretation of normal and pathologic physiology. The earnest student cannot fail to get excellent orientation as a neuroanatomist and neurologist.

Über nichthypophysäre Chiasmasyndrome. By M. Gil Espinosa. Pp. 60. Basel, Switzerland: S. Karger, Ltd., 1946.

This little monograph is a review of the various conditions, exclusive of primary tumor of the pituitary gland, capable of producing a chiasmal syndrome. It con-

tains nothing new and covers rather sketchily a large and complicated subject. No new material is contained within it except that the author adds to the usual suprasellar causes of the chiasmal syndrome cholesteatoma, granuloma, chordoma, angioma, chondroma and parasitic infections. The bibliography is inadequate.

Technic of Psychoanalytic Therapy. By Sandor Lorand, M.D. Price, \$2.50. Pp. 251. New York: International Universities Press, Inc., 1946.

This book is the outgrowth of Dr. Lorand's course in technic which he gives regularly at the New York Psychoanalytic Institute.

Outstanding in this book is the absence of any rigid rules. The author consistently stresses flexibility—flexibility implemented by a thorough personal analysis, as well as accumulative experience. However, this flexibility must take place within the framework of the freudian conception of psychodynamics.

Paramount emphasis is laid on the transference situation and its correct analysis. Thus, in chapters headed "Anxieties and Phobias," "Sexual Difficulties in the Male," "Sexual Difficulties in the Female," "Compulsion Neuroses" and "Neurotic Depressions," the author points out the patterns that transference takes in those clinical categories. The analyst must be ever sensitive to the transference situation and its correct analysis.

The author's chapter on countertransference reflects his great experience in psychoanalytic technic. As a training analyst, he has had the opportunity to observe the innumerable pitfalls of the young analyst, and in this chapter he records the stumbling-blocks which are encountered.

This book answers many questions, but leaves a good number unanswered. However, the psychoanalysts apparently do not intend to spoon-feed students. Too many broad statements are made which require better elaboration. Analysts, in building up a thesis, have a disconcerting manner of stating, "Of course, this means . . .," or "it is obvious that. . . ." The author is no exception. Unfortunately, those deductions are not so obvious as the author implies. It may be obvious to him and to other trained analysts, but certainly not to the student.

To those who have a good groundwork in freudian psychoanalysis, this book is highly recommended.

Physiologie oculaire clinique. By A. Magitot. Paper. Price, 750 francs. Pp. 458, with 230 illustrations. Paris: Masson & Cie, 1946.

Magitot has been interested in ocular physiology for the last forty years. His book on the iris (*L'iris*, Paris, Gaston Doin & Cie, 1921) is a classic, and he has published innumerable papers on various phases of ocular physiology, more particularly on the circulation of the eye and the regulation of ocular tension. He retired from active duty in the Lariboisière Hospital, of Paris, in 1940 and thus has been enabled to collect his papers and write this excellent book.

It is noticeable that it was written by an ophthalmologist, not a physiologist, for the author has constantly in mind the need of explaining clinical features.

There are fifteen chapters, some of which will be of interest only to ophthalmologists, but others are closely related to the field of neurology. Physiologic optics has purposely been left aside. Chapter 1 deals with the physiology of the lids and of lacrimation. Chapter 2 is devoted to the trigeminal nerve and the autonomic nerves and centers. In the next three chapters the author discusses at length the problems of ocular tension and nutrition, and in chapters 6 and 7, the physiology of the cornea and the conjunctiva. The next chapter, on the iris and pupil, is, of course, of particular interest to the neurologist. Chapters 9, 10 and 11 (on the lens and retina) are, again, more strictly ophthalmologic, but the last four chapters are those to which neurologists will mostly turn (chapter 12, the optic nerve and visual fields; chapter 13, the visual cortical area; chapter 14, oculomotor physiology, and chapter 15, binocular vision).

The numerous illustrations are excellent, there is a good index, and references are given at the end of each chapter.

- The Peripheral Circulation in Health and Disease.** Robert L. Richards, M.D.
Price, \$6. Pp. 153. Baltimore: Williams & Wilkins Company, 1946.

This book is an investigation into one aspect of the function of the autonomic nervous system—a study of peripheral circulation, mainly by the method of measurement of skin temperature. As such, there are two basic chapters on spontaneous and imposed variations in vasomotor activity, to which future workers using the skin temperature method will undoubtedly refer. They contain, in addition to a critical review of pertinent literature, a reevaluation of the influence of environmental temperature, basal metabolic rate, food, exercise, sleep and changes in posture on the temperature of the limb. They emphasize the concept of vasomotor gradient and describe the use of the limb immersion method as a relatively simple method of producing reflex vasodilatation and vasoconstriction. Diagnostic nerve block, reactive hyperemia and artificial pyrexia are also evaluated.

The clinical section of the book is disappointing if one expects full study of all aspects of peripheral circulatory disease; but, restricted though the book may be, important methods of study using skin temperatures are well presented and the value of such study in prognosis and treatment is indicated. Occlusive vascular disease and Raynaud's phenomenon are each considered as a whole. A chapter on vasomotor changes following complete and incomplete division of the peripheral nerve presents the clinical picture (warm and cold phases) and discusses interestingly the theoretic implications of the two phases. This chapter is based on a study of 350 patients with lesions of the main nerve trunks to the limbs and is a complete essay in itself, worth the reading. There is a final chapter on the immersion foot syndrome.

In all, this book is a careful clinical contribution to one phase of the study of the autonomic nervous system.

- Clinical Examination of the Nervous System.** By G. H. Monrad-Krohn.
Eighth edition. Price, \$4. Pp. 380, with 126 illustrations. London: H. K. Lewis & Co., Inc., 1947.

The middle-aged teacher of neurology has watched this exceptionally useful primer grow in the past twenty-five years from hip pocket to brief case size. It has lost none of its flavor, although with the excellent new illustrations some thought might be given to revising the truly ancient ones that have been inherited from the past. In his preface the author expresses his enthusiasm for neurology: "Whilst some twenty or thirty years back even in many civilized countries neurology was regarded only as a by-product of internal medicine or of psychiatry, it is today everywhere recognized as an independent branch of medicine of central importance. Everywhere the number of neurological and neurosurgical clinics is steadily increasing."

Considering that Norway was almost completely cut off from the outside world during the war, Monrad-Krohn has performed an excellent task in keeping up with the neurologic literature. This work makes no pretense to covering the field of clinical neurology; it is, rather, a clinical manual that the student may carry with him to the bedside for the exploration of a patient with disease of the nervous system. In this edition more emphasis is placed on ancillary investigations than has been done in past editions. Sections on roentgenography, encephalography and angiography, accompanied with excellent illustrations, enhance the value of the work and show what the well equipped neurologist should be able to obtain in the way of information from his patient. Myelography, however, is only briefly mentioned. The author adheres to his purpose in concentrating on localization and leaves the question of diagnosis of the nature of the lesion to the student of the larger books. When the student has definitely localized the disease process, the evolution and nature of the disease may become evident. The book can be read with pleasure as well as with profit, for the language is unaffected and clear.

DISSEMINATED ENCEPHALOMYELITIS EXPERIMENTALLY PRODUCED BY THE USE OF HOMOLOGOUS ANTIGEN

L. RAYMOND MORRISON, M.D.

BOSTON

THE ACUTE disseminated encephalomyelitis that sometimes follows vaccination against rabies¹ or smallpox,² as well as the post-infectious encephalomyelitis following exanthematous diseases, bears such an apparently close relation to multiple sclerosis, Schilder's disease (progressive subcortical encephalopathy) and other demyelinating processes in the central nervous system that it has attracted the attention of numerous investigators in recent years. But it was in 1895 that Pierre Marie³ first stressed the observation that multiple sclerosis frequently followed smallpox. The literature has been rather completely covered by Ferraro⁴ and the reader is referred to him for a bibliography dealing with phases of the problem that are beyond the scope of the present experiments.

As long ago as 1898, while studying the toxic effects of tissues of other species, during his investigations on diphtheria and on rabies, Centanni⁵ observed the untoward effects of saline suspensions of brain

Read before the Boston Society of Psychiatry and Neurology, April 17, 1947.

A part of the expense of this investigation was defrayed by the Commonwealth Fund.

From the Department of Neuropathology and the Robert W. Lovett Fund for the Study of Crippling Disease, Harvard Medical School, and the Neuropathology Laboratory, Massachusetts General Hospital.

1. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis: Clinicopathologic Study, *Arch. Neurol. & Psychiat.* **23**:1138 (June) 1930.

2. (a) Greenfield, J. G.: Acute Disseminated Encephalomyelitis, in Brown-ing, C. H., and others: *System of Bacteriology in Relation to Medicine*, Medical Research Council, London, His Majesty's Stationery Office, 1930, vol 3, pp. 133-139. (b) Milligan, R. M., and Neuburger, K.: Post-Vaccinal Encephalitis in Adults, *J. Neuropath. & Exper. Neurol.* **1**:416, 1942.

3. Marie, P.: *Lectures on Diseases of the Spinal Cord*, London, New Sydenham Society, 1895.

4. Ferraro, A.: Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain, *Arch. Neurol. & Psychiat.* **52**:443 (Dec.) 1944.

5. Centanni, E.: Sui prodotti tossici secondarii nelle infezioni, *Riforma med.* **3**:637, 1898.

injected into rabbits. He reported prostration and toxemia. Hurst⁶ was among the first of the present day investigators to observe paralysis in rabbits following repeated subcutaneous or intramuscular injections of saline suspensions of human brain. He found no paralysis following injections of brain of the guinea pig, sheep or monkey. Detailed histologic examination of the nervous system revealed no microscopic lesions in any of these animals. The brain tissue he injected was normal, slightly denatured by mild heat or phenolized. The next year (1933) Rivers, Sprunt and Berry⁷ produced clinical neurologic disease in monkeys with repeated injections of extracts and saline suspensions of normal rabbit brain, and they also observed histologic evidence of encephalomyelitis with demyelination in the affected monkeys. Shortly thereafter Rivers and Schwentker⁸ elaborated on this work and presented detailed histologic descriptions which have served as the basis of comparison for the work that has been done since. In 1940 Ferraro and Jervis⁹ repeated and confirmed the work of Rivers and his co-workers. By using saline suspensions and alcohol-ether extracts of rabbit brain, they were able to produce encephalomyelitis in monkeys after repeated intramuscular injections. The monkeys received between twenty-nine and one hundred and three injections during the course of from one hundred and twelve to four hundred and five days. After a minimum of one hundred days all 7 monkeys in their series presented clinical symptoms referable to the nervous system, such as forced position of the head, tremors, nystagmus and spastic paresis. Histologically these animals, like those of Rivers and co-workers, showed many small lesions disseminated throughout the central nervous system, more particularly but not exclusively, in the white matter. Most of the lesions were perivascular and were characterized by loss of myelin and axons and by sleeves of hematogenous cells, or hematogenous and interstitial cells, in the zone immediately adjacent to the involved blood vessels. A noteworthy feature of the exudate was the presence of multinucleated giant cells, which had also been reported previously by Rivers and Schwentker.⁸

6. Hurst, E. W.: The Effect of Injection of Normal Brain Emulsions into Rabbits, with Special Reference to the Etiology of the Paralytic Accidents of Antirabic Treatment, *J. Hyg.* **32**:33, 1932.

7. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, *J. Exper. Med.* **58**:39, 1933.

8. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, *J. Exper. Med.* **61**: 689, 1935.

9. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, *Arch. Neurol. & Psychiat.* **43**:195 (Feb.) 1940.

The mechanism of the production of these lesions offers a fruitful field for speculation. It has been known for some time¹⁰ that fresh, homologous brain tissue possesses little or no antigenic power. It is also well known that heterologous brain,¹¹ as well as homologous brain plus pig serum,¹⁰ is capable of inciting in animals receiving them antibrain antibodies, which can be demonstrated either by the precipitin or by the complement fixation test. In 1934, in order to see whether brain haptene could be converted into a complete antigen without the addition of heterologous protein, Schwentker and Rivers¹² autolyzed sterile homologous brain tissue, which, when injected into rabbits, was definitely antigenic. In like manner, they also found that emulsions of fresh, homologous brain when infected with vaccine virus was likewise antigenic, as demonstrated by the complement fixation and the precipitin test. They further showed that embryonic and neonatal brain tissue was nonantigenic and that antigenicity increased with age and reached its maximum at maturity. Fitting in with this demonstration was the observation that the antigenicity of the white matter was about six times as great as that of the gray matter. This important investigation points to the antigenic character of the modified myelin sheath; and, because of the subsequent demyelination accompanying experimentally produced encephalomyelitis, speculation is in order as to the possibility of the involvement of a lipid antigen in such conditions as multiple sclerosis and other demyelinating diseases.

Another point may be mentioned at this time. As long ago as 1924 Lewis and Loomis¹³ showed that antibody titers to substances not related to tubercle bacilli were considerably higher in tuberculous guinea pigs than they were in normal animals. Dienes and Schoenheit¹⁴ discovered that when egg white or horse serum was injected into a tuberculous focus, such as a tuberculous gland, the sensitization to these antigens was more vigorous in that the cutaneous reactions to

10. Lewis, J. H.: Immunologic Specificity of Brain Tissue, *J. Immunol.* **24**: 193, 1933.

11. Witebsky, E., and Steinfeld, J.: Untersuchungen über spezifische Antigenfunktionen von Organen, *Ztschr. f. Immunitätsforsch. u. Exper. Therap.* **58**: 271, 1928.

12. Schwentker, F., and Rivers, T. M.: Antibody Response of Rabbits to Injections of Emulsions and Extracts of Homologous Brain, *J. Exper. Med.* **60**: 559, 1934.

13. Lewis, P. A., and Loomis, D.: Allergic Irritability: Influence of Chronic Infections and of Trypan Blue on Formation of Specific Antibodies, *J. Exper. Med.* **43**:263, 1926.

14. Dienes, L., and Schoenheit, E. W.: Local Hypersensitiveness in Tuberculous Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **24**:32, 1926; Reproduction of Tuberculin Hypersensitiveness in Guinea Pigs with Various Protein Substances, *Am. Rev. Tuberc.* **20**:92, 1929.

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these antigens appeared and disappeared more slowly and were sometimes necrotic. Dienes¹⁵ was then able to produce the same enhanced reaction by using dead tubercle bacilli. This adjuvant technic was carried on from that point by Freund and his co-workers¹⁶ with the use of killed tubercle bacilli, liquid petrolatum and sometimes "aquaphor" (an oxycholesterol-petrolatum ointment base), obtaining long-sustained and sometimes necrotic cutaneous reactions to antigens not related to tubercle bacilli. Using the adjuvant technic of Freund, Kopeloff and Kopeloff¹⁷ succeeded in producing antibrain antibodies in the serum of monkeys immunized to sheep brain. Making use of the same technic while working on poliomyelitis, Morgan¹⁸ recently produced encephalomyelitis in the monkey. Heat-killed tubercle bacilli in "falba"^{18a} with homologous central nervous system tissue caused extensive encephalomyelitis in 7 out of 12 monkeys, while 8 out of 9 monkeys presented similar lesions after injections of these adjuvants mixed with spinal cord infected with virus of poliomyelitis. The adjuvants alone or with other organs produced no such disease in the central nervous system. Even more recently, Kabat, Wolf and Bezer,¹⁹ also utilizing the adjuvant technic, but employing heterologous antigen, succeeded in hastening the reaction time in the production of encephalomyelitis in monkeys.^{19a}

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16. Freund, J., and McDermott, K.: Sensitization to Horse Serum by Means of Adjuvants, *Proc. Soc. Exper. Biol. & Med.* **49**:548, 1942. Freund, J., and Bonato, M. V.: The Effect of Paraffin Oil, Lanolin-Like Substances and Killed Tubercle Bacilli on Immunization with Diphtheria Toxoid and Bact. Typhosum, *J. Immunol.* **48**:325, 1944.

17. Kopeloff, L. M., and Kopeloff, N.: The Production of Antibrain Antibodies in the Monkey, *J. Immunol.* **48**:297, 1944.

18. Morgan, I.: Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Cord, *J. Bact.* **51**:53, 1946.

18a. "Falba" (Pfaltz and Bauer Inc., New York), a hydrous wool fat-like adsorption base, said to be a mixture of beeswax, paraffin oils of varying viscosities and oxycholesterol extracted from hydrous wool fat.¹⁸

19. Kabat, E. A.; Wolf, A., and Bezer, A.: Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Brain Tissue with Adjuvants, *Science* **104**:262, 1946.

19a. Since this article was submitted for publication, new papers by Morgan and by Kabat and associates have appeared: Morgan, I. M.: Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Nervous Tissue, *J. Exper. Med.* **85**:131, 1947. Kabat, E. A.; Wolf, A., and Bezer, A. E.: The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous and Homologous Brain Tissue with Adjuvants, *ibid.* **85**:117, 1947.

A further point may be noted here. It has been recently shown that the toxic filtrate (alpha toxin) of *Clostridium welchii* (perfringens) causes demyelination in vitro.²⁰ This alpha toxin contains, among other factors, a large percentage of an enzyme capable of hydrolyzing lecithin.²¹ Under certain optimum conditions²⁰ the lecithin of the myelin sheath can be hydrolyzed, leaving the remainder of the myelin intact, thus producing a slightly abnormal myelin sheath.

It is clear from this short review that encephalomyelitis may be experimentally produced in laboratory animals by the repeated injections of heterologous brain antigen and that, as shown serologically, antibrain antibodies have been produced with the use of homologous antigen that has been changed by autolysis or made effective by the addition of adjuvants. It is likewise clear that normal adult heterologous brain tissue, especially white matter, is definitely antigenic, as shown by serologic reaction. With these ideas in mind, the present work was undertaken. It was believed that if there is any relation between the facts previously mentioned and demyelinating diseases as seen in man, the question of heterologous antigen is patently too artificial to be of universal value. The possibility of becoming inoculated with the nervous system of another species, except during the Pasteur treatment or some such special condition, is remote. But the possibility of autoantigen being derived from the patient's own nervous system has to be considered.

The purpose of the present paper is to report on the histologic nature of encephalomyelitis as it has been produced in rabbits with the use of homologous antigen.

MATERIALS AND METHODS

Antigen was prepared in five different ways. With all forms only the spinal cord was used on account of its relatively high content of white matter. In preparation of the first four types of antigen the spinal cord of the rabbit was aseptically removed, and then, after removal of most of the meninges, the cord was ground up in a mortar, care being exercised to keep the procedure as aseptic as possible. The first antigen, called "normal rabbit cord," was merely suspended in isotonic solution of sodium chloride, and a 0.3 per cent solution of phenol was added as a preservative. The second antigen, called "Welch toxin antigen," was prepared as follows: After the rabbit cord was ground up aseptically, it was thoroughly mixed with an equal volume of the toxic filtrate (alpha toxin) of *Cl. welchii*²² and incubated at 37 C. for twenty-four hours. Then isotonic solution

20. Morrison, L. R., and Zamecnik, P. C.: Experimental Demyelination by Means of Enzymes, with Special Reference to the Alpha Toxin of *Cl. Welchii*, to be published.

21. Macfarlane, M. G., and Knight, B. C. J. D.: Biochemistry of Bacterial Toxins: I. Lecithinase Activity of *Cl. Welchii* Toxin, *Biochem. J.* **35**:884, 1941.

22. Glycerinated *Cl. welchii* (type A) filtrate, different batches of which have assayed as containing from 500 to 1,700 mouse subcutaneous minimal lethal doses per cubic centimeter, was obtained from Dr. Paul C. Zamecnik.

of sodium chloride was added to the mixture, and it was centrifuged for ten minutes. The supernatant fluid was decanted and fresh saline solution added. After a thorough mixing, the suspension was centrifuged again. This procedure was carried out three times, or until the supernatant fluid was clear and colorless. This suspension of residue in isotonic solution of sodium chloride was used as the antigen and was believed to contain "modified" myelin sheath. The third antigen, called "no. 3 antigen," was prepared by incubating normal rabbit spinal cord in the filtrate of *Cl. welchii* as in the preparation of the second antigen, but the Welch toxin was not removed. After incubation for twenty-four hours, isotonic solution of sodium chloride was added to the mixture to make a suitable dilution, and this suspension was used as the antigen. Welch toxin antigen and no. 3 antigen were phenolized in the same way as the normal rabbit cord antigen. The fourth antigen, called the "tubercle bacillus antigen," was prepared by mixing 2 cc. of ground rabbit cord with a suspension in 4 cc. of "bayol F"^{22a} of tubercle bacilli killed in solution of formaldehyde U. S. P. The fifth antigen consisted of normal human spinal cord treated with solution of formaldehyde U. S. P. After removal of the cord from the meninges, small blocks were ground up in a mortar and suspended in 0.1 per cent concentration of solution of formaldehyde U. S. P. in isotonic solution of sodium chloride. The fourth antigen was used freshly prepared. The others were kept frozen on solid carbon dioxide except when in use. The first three antigens were administered intradermally on two successive days each week. One cubic centimeter of the suspension was injected in a series of eight or ten wheals on the abdominal skin, from which the hair had been plucked. When the no. 3 antigen was fresh, before the enzyme had exhausted itself on the substrate, a slight necrotizing effect was produced at each needle hole. This invariably healed in the course of a week or two. The "tubercle bacillus antigen" was given into the foot pads of the rabbit, 0.1 cc. in each foot, so that each animal received only one set of injections, totaling 0.4 cc. per animal. These injections were not repeated week after week. They were given but once. The human cord (treated with solution of formaldehyde U. S. P.) was administered intraperitoneally, three times a week, about 5 cc being given in each injection.

Animals of the first series, inoculated with normal rabbit cord antigen, were not expected to show any signs of disease of the nervous system. They were used as a partial control on animals of the second and third series, which were inoculated with modified homologous spinal cord. As a further control on the series receiving the Welch toxin antigen, glycerinated Welch toxin without the spinal cord might have been administered intradermally in semiweekly injections; such controls were not used, however, because of the severe local dermonecrosis produced, even if the animals could have survived the hemolytic effect of the enzyme. Used as a partial control, however, were mice, rabbits and dogs of another experiment which received repeated sublethal doses of *Cl. welchii* filtrate subcutaneously, intramuscularly and intravenously, without producing any clinical or histologic signs of encephalitis.

Either the animals were killed by the intravenous injection of air or they died. The brain and spinal cord were removed immediately after death, or early in the morning if the rabbit died during the night. Sections from different parts of the central nervous system were stained by a variety of methods after appropriate fixation. Among the most common technics used were the Nissl, hematoxylin

22a. "Bayol F" (Standard Oil Company) is liquid petrolatum, with a specific gravity of 0.825 at 60 F. and a viscosity of 50 to 55 at 100 F.

and eosin and Van Gieson stains; the Hortega method for microglia; the Cajal method for astrocytes; the Weil method for myelin sheath; oil red O for fat, and the Bodian method for axons. These stains were used routinely and were augmented by others when necessary.

EXPERIMENTS

The experiments can be divided into five groups according to the antigen used. The first four series of rabbits received injections of rabbit cord, while the fifth had injections of human cord. The animals in the first series (table 1) presented no clinical symptoms referable to the nervous system. Rabbit 10 exhibited *Pasteurella* infections on

TABLE 1.—*Suspension of Normal Rabbit Spinal Cord in Isotonic Solution of Sodium Chloride*

Rabbit Number	Number of Injections *	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
10	95	348	—	—
13	105	392	—	—
991	104	390	—	—

* Since only about 0.1 cc. could be injected in one wheal, about ten needle holes were made in administering 1 cc. of antigen. This 1 cc. was called one injection.

TABLE 2.—*Rabbit Spinal Cord Incubated in Welch Filtrate, Toxin Removed*

Rabbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
29	54	195	+	+
36	55	540	—	—
42	1	8	+	+

the hindfeet, which were troublesome; so she was killed just under a year after the first inoculation.

Rabbit 42 (table 2) had but one injection, receiving 1 cc. of the antigen in eleven intradermal wheals. This antigen was freshly prepared, but after the animal was given the injection it was discovered that the preparation was not sterile; consequently, that tube of antigen was discarded. During the course of the next few days, pending the preparation of a new antigen, this rabbit manifested symptoms referable to the nervous system. The right hindleg was weak and was moved awkwardly. The rabbit slipped and fell to one side when it attempted to hop. The reflexes were increased usually, but sometimes they were difficult to elicit, especially in the right hindleg. Gradually the animal appeared more ill. Her coat was neglected; her ears drooped; she moved about less and less, ate nothing and died eight days after the inoculation. Before that time she had apparently been well.

Rabbit 29 exhibited weakness in both front paws about a week after the first inoculation. The paws flared out sideways and were drawn in awkwardly when the rabbit attempted to hop. This condition improved gradually, but the rabbit never fully recovered the complete use of the front paws. About a month after the first inoculation the animal was seized with a violent convulsion during the procedure of inoculation. This convulsion lasted about two minutes and was generalized, involving all four legs and the head and trunk. It was never repeated so far as we observed. About two months after the first injection a shaky, quivering incoordination of the hindlegs developed. This was transient and in two or three days had disappeared. The only possible sign of involvement of the nervous system that the rabbit retained was slight weakness of the front paws. It seemed unlikely that other neurologic signs would develop; so the animal was killed about six months after the first inoculation. Rabbit 36 never presented any untoward clinical signs. The injections were

TABLE 3.—*Rabbit Spinal Cord Incubated in Welch Filtrate, Toxin Retained*

Rabbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
16	63	238	—	+
50	12	160	—	—
104	6	19	+	+
54	12	160	—	—
308	65	347	—	+

discontinued after six months, and the animal was allowed to have a long survival time, in view of the histologic changes in rabbit 29, which had almost no clinical signs for three months before death.

Only 1 of the animals in the third series (table.3) presented clinical signs that could be definitely associated with the nervous system. Rabbit 104, after six injections, showed weakness and awkwardness of the hindlegs. The tendon reflexes were equal on the two sides, but were sluggish and not always obtainable. This weakness was progressive, and a day or two after its first appearance the rabbit dragged herself about with her forepaws, the hind extremities extending out behind. There was not complete paralysis, however, for the animal could hop in a feeble way when stimulated, after her hindlegs had been passively bent into the hopping position. The animal ate but little, became weaker, neglected her coat and died during the night, five days after the first clinical sign. Rabbit 16 also exhibited awkwardness of the right hindleg, incoordinated movements when hopping and an apparent paresis in both hindlegs. But these signs were probably caused by an abscess in the right groin, which was discovered a day or two before the animal was killed.

The animals of the fourth series (table 4) had a much prompter response. Nine out of the 10 rabbits presented clinical signs, most of them neurologic. Rabbit 435 presented no untoward signs and was alive and well five months after the inoculation. Rabbits 464 and 471 appeared sleepy, apathetic and off their diet; they neglected their coat, failed to hold their ears erect and moved about only when they were prodded. There was no apparent paresis, however. They both died suddenly, about two weeks after the injection. All the other animals of this group presented symptoms referable to the nervous system. Sometimes the front legs would be affected first, and, because of the weakness in them, the animal would fall forward on its chest, the forepaws being unable to support the weight of the body. In such circumstances the front paws would extend out laterally in a splayed fashion, and when they were moved it was in an awkward, uncoordinated

TABLE 4.—*Rabbit Spinal Cord Mixed with Killed Tubercle Bacilli in Liquid Petrolatum* ^{22a}

Rabbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
433	1 set	23	+	+
435	1 set	165	—	—
441	1 set	56	+	+
452	1 set	21	+	+
463	1 set	119	+	+
464	1 set	16	—	+
466	1 set	131	+	+
471	1 set	14	—	—
472	1 set	16	+	+
487	1 set	21	+	+

manner. Usually, however, the hindpaws were most affected. Weakness, incoordination and, in a few cases, especially in the right hindleg of rabbit 463, complete paralysis were the common signs. The animal was ataxic, falling about or sliding along the side of the pen by leaning on the wall. The reflexes were usually present, even in severely paretic limbs, and response to deep pinprick was thought to be in the nature of a reflex response. In a few animals, notably rabbit 463, clonus of the hindleg could be elicited if the foot was supported by the examiner's hand while the tendons were tapped gently with the hammer. In fact, the whole body was often hyperkinetic, and, especially in the early stage of involvement of the nervous system, if the rabbit, while sitting on the floor, was unexpectedly touched with the examiner's foot, the animal would leap violently several feet forward. In a few animals clearcut neurologic signs appeared early, and later practically disappeared. This was true especially of rabbit 433. She showed great incoordination, tumbling all over herself when she hopped, falling and leaning against the wall, sometimes as though she were blind (the pupils

reacted to light), later dragging her hindquarters about by the exclusive use of the front paws. These signs gradually subsided, and for a day or two before she was killed she presented scarcely any neurologic abnormalities.

The fifth group of rabbits (table 5) is included for purposes of comparison because of the similarity of clinical signs and histologic changes. There were 5 other rabbits of this series, each of which received fewer than thirty-seven injections of the heterologous antigen treated with solution of formaldehyde, U. S. P. They all presented clinical signs referable to the central nervous system, and they all died in less than three months. The clinical signs were similar in all 6 animals and consisted in weakness of the hindlegs, incoordination, ataxia, presence of and sometimes increase in reflexes, loss of appetite, and loss of weight, followed by extreme generalized weakness, gasping for breath and, finally, death. Rabbit 398 was killed with ether while in extremis. Owing to circumstances beyond my control, the nervous

TABLE 5.—*Suspension in Saline Solution of Human Spinal Cord Treated with Dilute Solution of Formaldehyde*

Babbit Number	Number of Injections	Survival Time, Days	Signs Referable to Central Nervous System	Pathologic Changes
398	37	92	+	+

systems of the other 5 animals of this series were not worked up histologically.

PATHOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM

• In view of the changes observed by previous investigators, who used unmodified homologous antigen, it was not expected that any pathologic changes would appear in animals 10, 13 and 991, but, as previously mentioned, they were used as a control for the other series. Histologic examination of their brains and cords revealed nothing abnormal. There was nowhere any sign of inflammation or demyelination, and these animals had received the greatest number of injections.

The remaining groups, however, all presented histologic disease of varying degrees of intensity. The lesions were so similar in most instances that they will, in general, be described collectively, emphasis being placed on specific differences as they arise. An underlying meningoencephalomyelitis was observed in the whole series of affected animals. Sometimes the disease was almost exclusively limited to the spinal cord, sometimes to the brain, but usually lesions could be observed disseminated throughout the central nervous system. There was probably, especially in the spinal cord, a greater tendency toward involvement

of the white matter, but lesions of the gray matter were not uncommon, particularly in the brain stem and in the cerebral cortex. These parenchymatous lesions were usually perivascular foci of infiltrating and reacting cells, seen especially around small veins and, to a lesser extent, around arteries, venules, arterioles and capillaries. There was no special predilection for the periventricular regions.

The meningitis was most pronounced in the animals of the series receiving the tubercle bacillus antigen, in which it was observed in the spinal cord in all rabbits, showing pathologic changes; but it was present in a mild way in either the cord or the brain, especially on the basilar



Fig. 1 (rabbit 433).—Meningitis, with the reaction involving the anterior spinal veins. The infiltration was chiefly lymphocytic, with occasional plasma cells and monocytes. Nissl stain: $\times 400$.

surface or around the cerebellum, in most of the affected animals of whatever series. When the meningitic reaction was mild, a thin layer of lymphocytes, with occasional plasma cells, lay in the meshes of the pia-arachnoid in a patchy distribution. In rabbits with severer involvement, as in rabbit 453 (fig. 1) with early lesions, the walls of the accessory anterior spinal veins and the posterior spinal veins were densely infiltrated with eight or ten layers of lymphocytes, while in the neighboring subarachnoid space great numbers of lymphocytes and monocytes with occasional eosinophils were present. In the animals

with old lesions, such as rabbits 441, 463 and 466, the pia-arachnoid had become slightly thickened and, although the exudate had subsided, the connective tissue had proliferated. This was true, too, over the basilar surface of the brain, as well as in the spinal cord.

Beneath the pia, in the parenchyma of the rabbits receiving the tubercle bacillus antigen, whether they presented a brisk meningitis or not, there was a vigorous reaction of microglia around the edge of the cord. Indeed, in some cases a strong microglial hyperplasia was present on the periphery of the cord when no inflammation could be seen in the meninges.

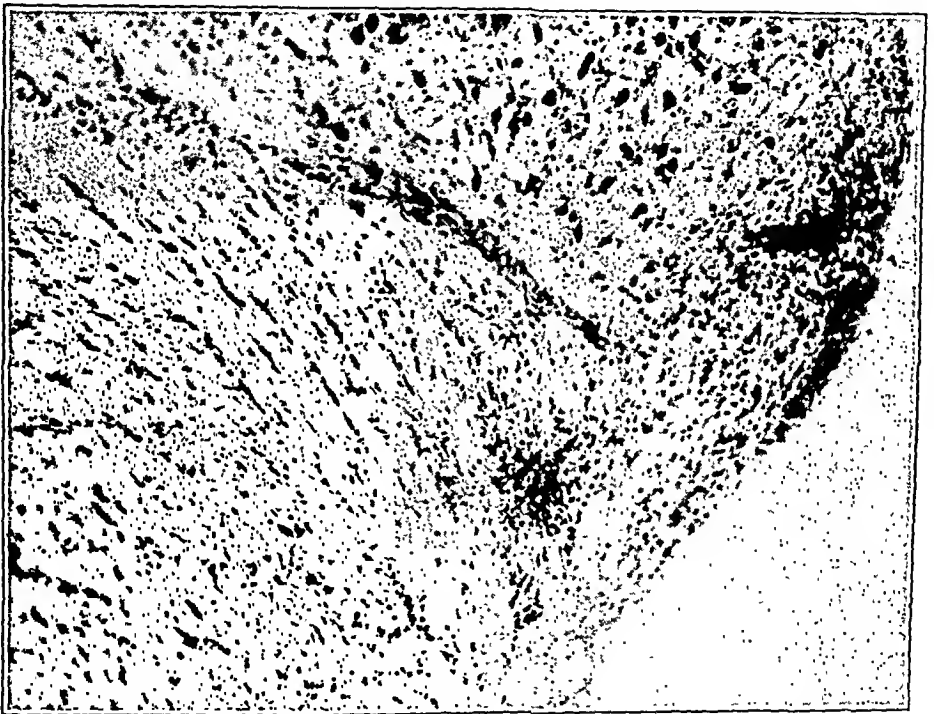


Fig. 2 (rabbit 104).—Perivascular foci of lymphocytes and microglia cells in the medulla. Nissl stain; $\times 100$.

The inflammatory reaction followed the blood vessels as they dipped from the subarachnoid space into the substance of the spinal cord, and in the brain perivascular foci could be seen, as previously stated, in various regions remote from both meninges and ventricles. This was not an equivocal reaction but a good, vigorous response (fig. 2). Occasionally the walls of the vessel itself were infiltrated with lymphocytes; if not, the Virchow-Robin space usually contained lymphocytes, a few plasma cells and histiocytes, and even occasionally a few polymorphonuclear leukocytes. But the chief reaction was outside the Virchow-Robin space, in the parenchymatous tissue, where microglia cells in abundance were the common feature; and it is desired to emphasize

this observation (fig. 3). The microglia cells were in various degrees of activation. In some instances they had small, sausage-shaped nuclei and long spikelike processes, only slightly swollen at the base, as seen in the Hortega, or in some circumstances in the Nissl, stain. In other instances, particularly in rabbits 463 and 466, frank compound granular corpuscles were present in profusion. These cells were seen not only in the parenchyma but also as collars of fat-laden gitter cells in the perivascular space. This combination of hematogenous cells and microglia-cytes was characteristic of the lesions throughout the series. Sometimes one type of cell predominated; sometimes the other. The type of cell that predominated was not determined by the case or by the

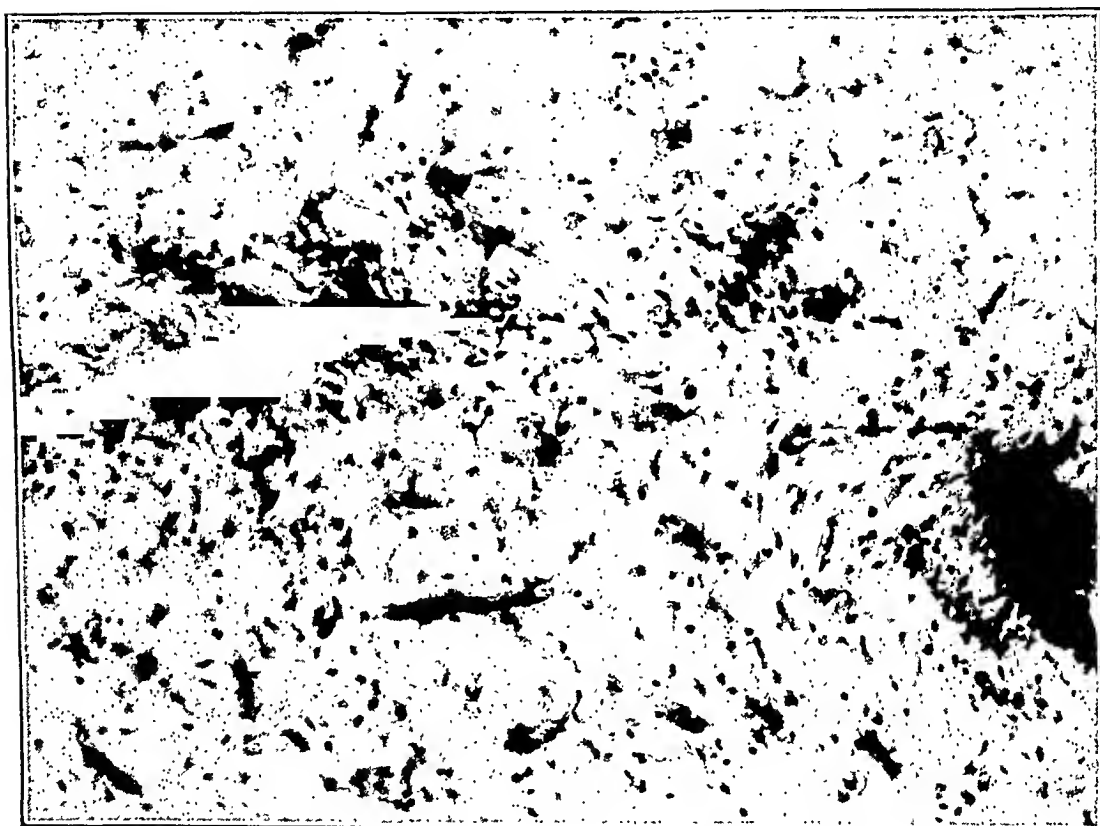


Fig. 3 (rabbit 487).—Perivascular foci of hematogenous cells and microglia-cytes in the spinal cord. Nissl stain; $\times 100$.

location. In rabbit 29, for example, in the brain could be seen occasional lesions composed practically entirely of hematogenous cells, other lesions in which only pleomorphic microglia cells were congregated around the blood vessel and still other lesions in which the microglia cells were scattered among the lymphocytes (fig. 4). In the spinal cord of animal 463, on the other hand, could be seen foci of large numbers of microglia cells in a low degree of activation; other foci presented fat-laden granular corpuscles, microglia cells in a relatively resting stage and lymphocytes.

In the immediate zone of this exudative reaction there was often destruction of myelin. This was more likely to occur when the reacting cells were microgliocytes or a combination of microgliocytes and hematogenous cells. If lymphocytes alone made up the perivascular cuffing, the loss of myelin was not noticeable, but when microglia participated in the reaction, even though the stage of activity represented by the compound granular corpuscles was not reached, there was perivascular loss of myelin, as seen in Weil's stain. This was not extensive destruction of (fig. 5) myelin; it was limited virtually to the zone occupied by the reacting cells and was usually about two or three times the diameter

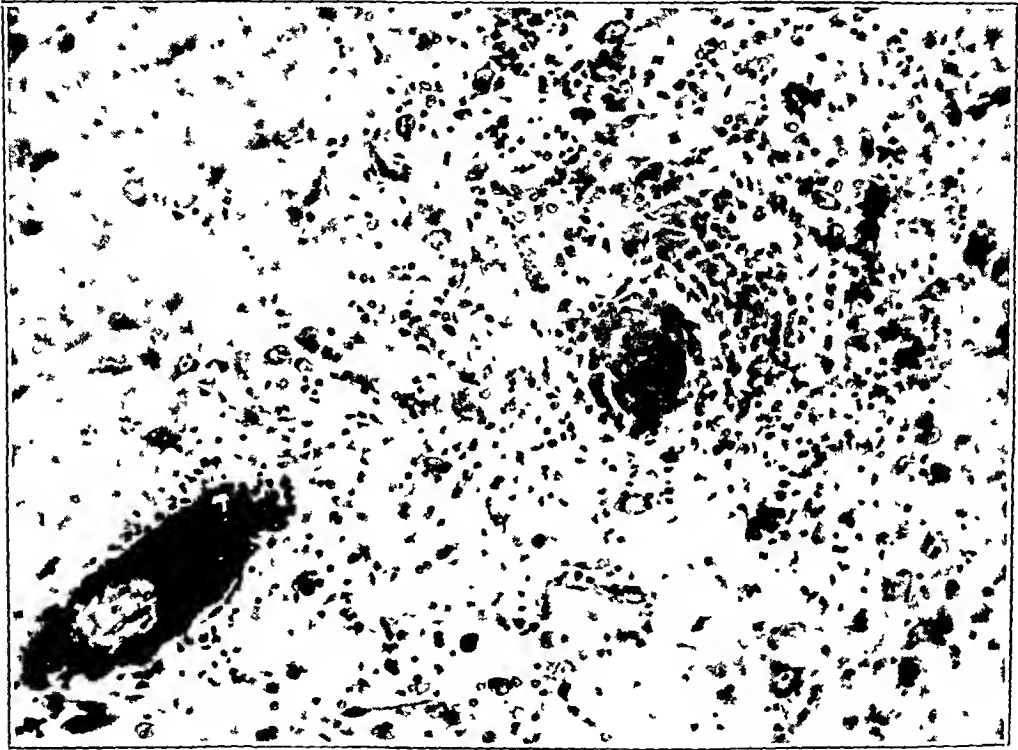


Fig. 4 (rabbit 29).—Perivascular reaction of hematogenous cells and microgliocytes. Nissl stain; $\times 200$.

of the blood vessel it surrounded. When vessels were close together, the inflammatory process pervaded them all, and the confluent patches of demyelination were, consequently, more conspicuous (fig 8, upper part). In lesions that had existed for some time, two weeks or more, it was easy to detect fat in sections stained with oil red O. The animals receiving the tubercle bacillus antigen offer the best instances of this. In figure 6 can be seen the dense hyperplasia of microglia with the Nissl stain. These cells, with abundant, foamy cytoplasm, were practically all in the gitter cell stage. In the oil red O preparation they appeared filled with brilliant red fat. With the Hortega stain the

cells were seen to have no, or at most only the slightest vestiges of, processes. With Weil's stain this region of the cord, of course, appeared completely demyelinated.

The blood vessels presented various degrees of occlusion, which in long-standing lesions reached serious proportions, as in some of the foci observed in rabbit 29. Infiltration of the wall of the blood vessel with round cells has already been mentioned; in addition, there were many instances of hyperplasia of the intima, with swelling and piling up of the endothelium, so that the lumen was frequently considerably constricted, if not completely occluded (fig. 9). Proliferation of the subendothelial connective tissue, together with adventitial over-



Fig. 5 (rabbit 487).—Small perivascular patches of demyelination in the spinal cord. Weil stain; $\times 400$.

growth, gave many of these vessels thick walls. Rabbits 29 and 398 presented blood vessels with thickened walls and greatly constricted lumens more frequently than other animals.

With regard to rabbit 398, which had received the human cord antigen, it may be said that the pathologic picture was very similar to that seen in the rabbits of the other series. A few points of difference, chiefly of degree, were noted. The lesions in this case were more definitely confined to the white matter, not only in the spinal cord but also in the brain. The cerebral peduncles (fig. 10), the internal capsule,

the centrum semiovale and the corpus callosum were conspicuously spotted with dense collars of microgliaocytes and round cells around the blood vessels in the perivascular spaces, and in the walls of the vessels, while the vessels so affected in the gray matter were distinctly fewer and the reaction was milder. There were, however, excellent, although fewer, lesions in the gray matter of the cervical portion of the cord and of the thalamus. Giant cells, that is, large cells with four or five nuclei, were seen occasionally in rabbit 398, not only in the meninges but also in the midst of other reacting cells in the tissue of the cord itself. These giant cells were seen occasionally, but rarely, in other rabbits, and usually only in the meningeal reaction.

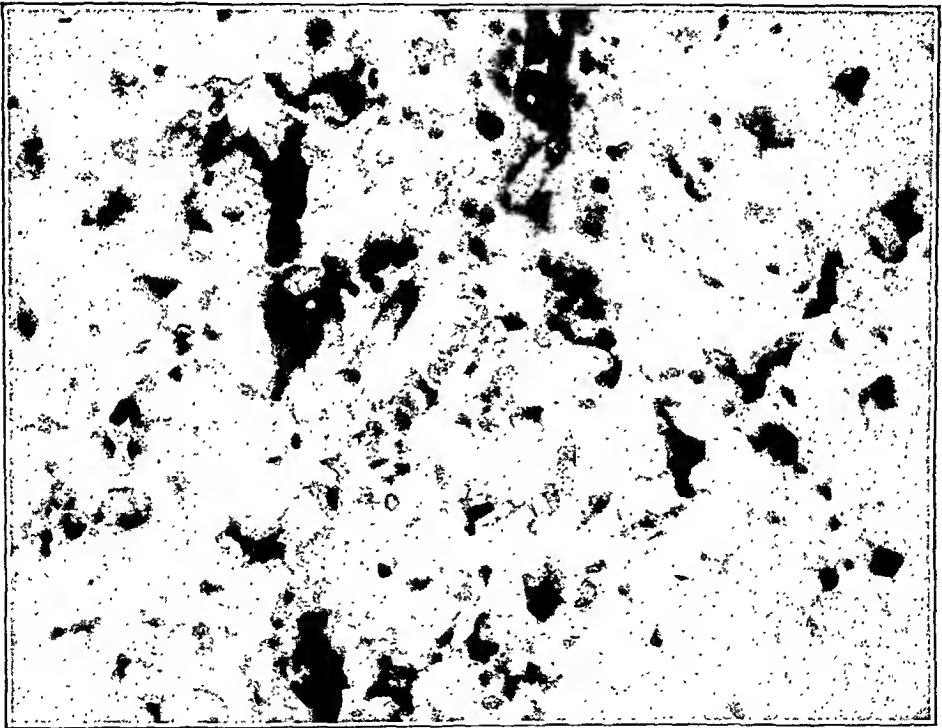


Fig. 6 (rabbit 463).—Compound granular corpuscles in the white matter of the spinal cord. Nissl stain; $\times 400$.

A point of similarity between the pathologic picture in this rabbit and that in the rabbits in the three preceding series was that when conspicuous lesions occurred in the spinal cord the posterior column was most severely affected. The degeneration extended usually around the edge of both lateral halves of the posterior funiculus, meeting in the midline and spreading ventrally along the raphe. This degeneration consisted not only in the inflammatory reaction but in fatty degeneration, as seen with the oil red O stain, and in demyelination, as seen with Weil's stain, as well.

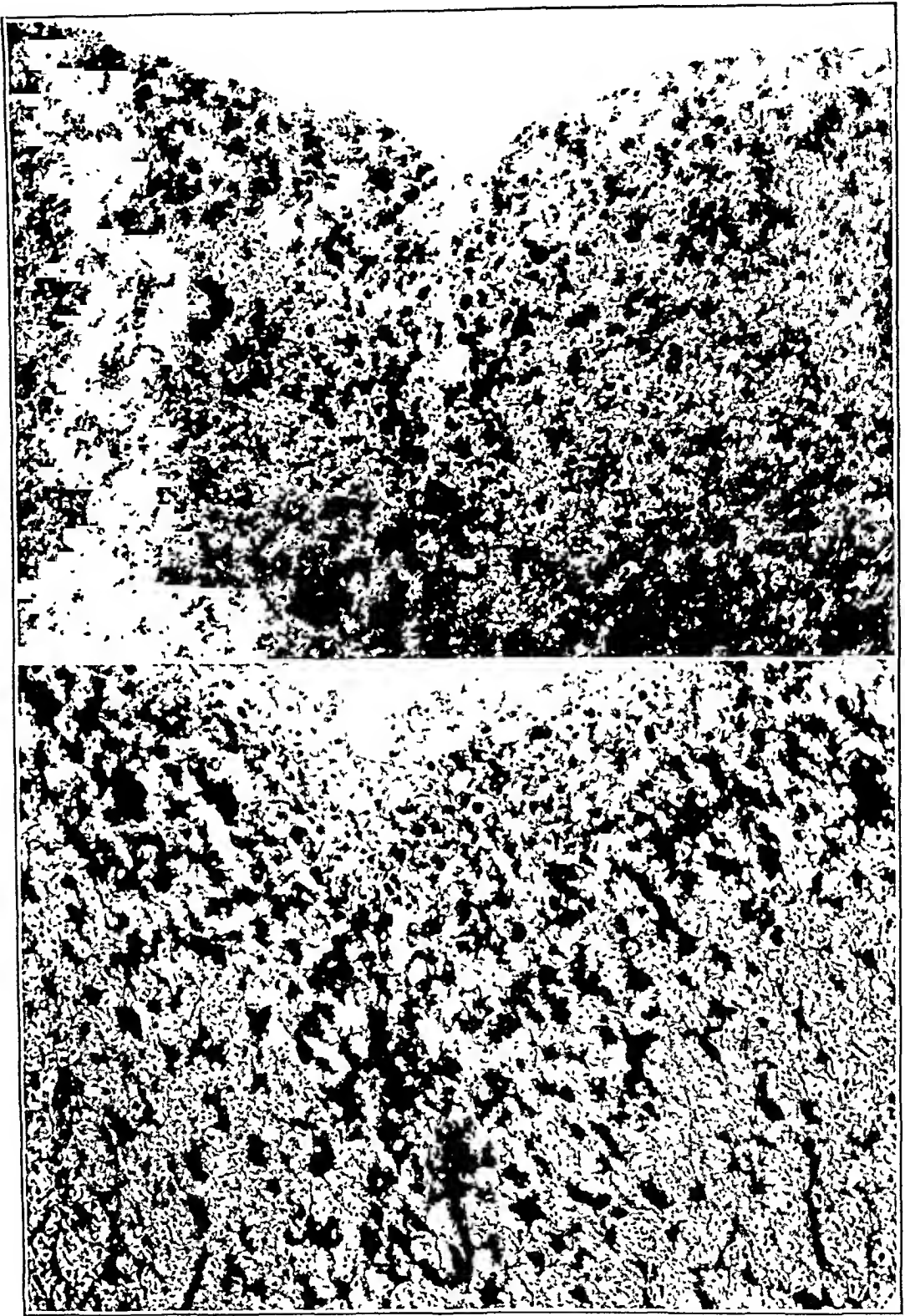


Fig. 7 (rabbit 463).—Transverse sections of the spinal cord, showing disease of the posterior columns. Upper portion, oil red O stain; $\times 200$. Lower portion, microglia in gitter cell formation; Hortega stain; $\times 200$.

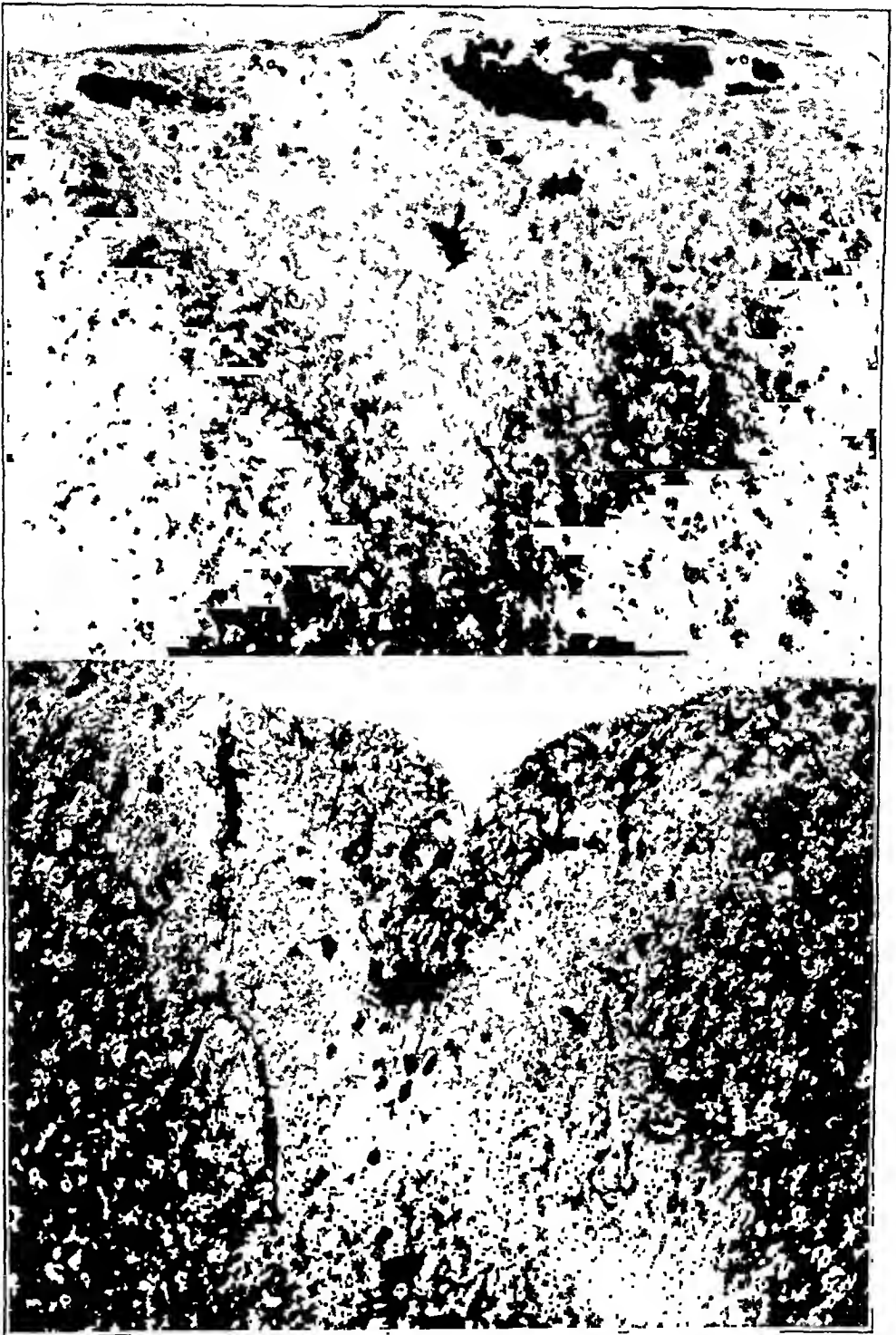


Fig. 8 (rabbit 463).—Transverse sections of the spinal cord, showing disease of the posterior columns. Upper portion, demyelination; Weil stain; $\times 200$. Lower portion, gliosis around the periphery; Cajal gold chloride-mercury bichloride stain; $\times 200$.

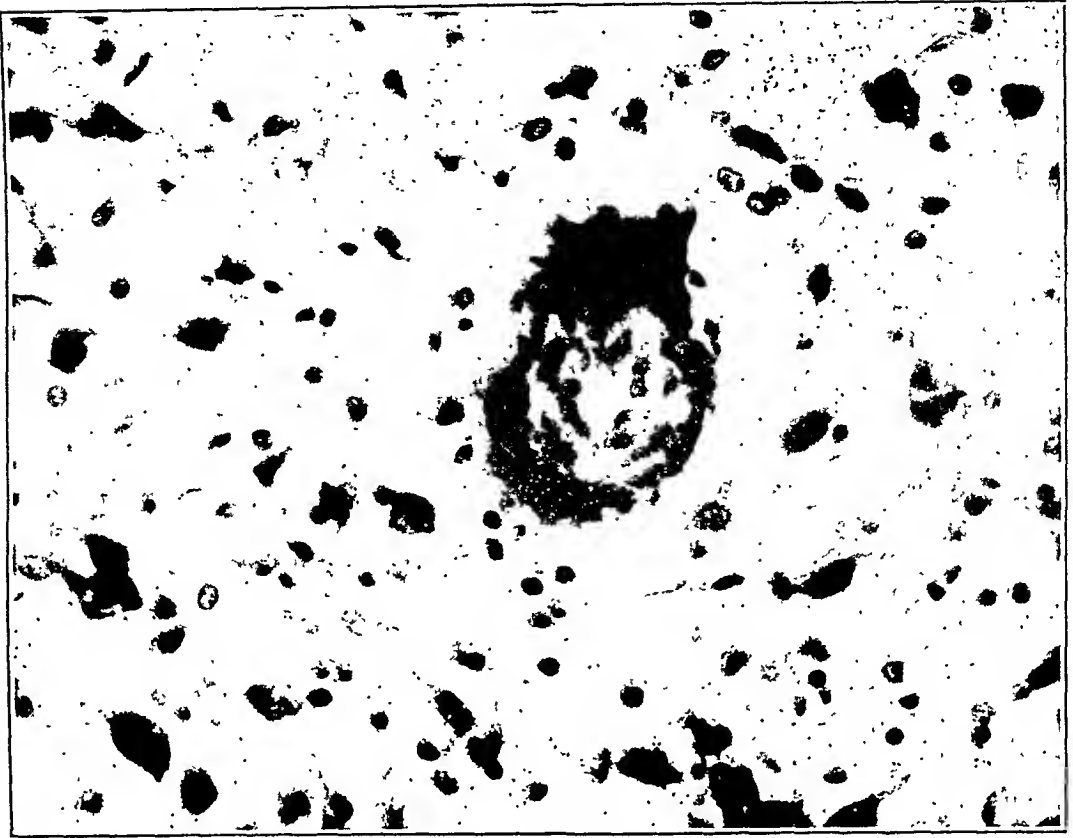


Fig. 9 (rabbit 29).—Infiltration of the adventitia, hyperplasia of the intima, swelling of the endothelium and constriction of the lumen of a small vein in the midbrain. Nissl stain; $\times 400$.

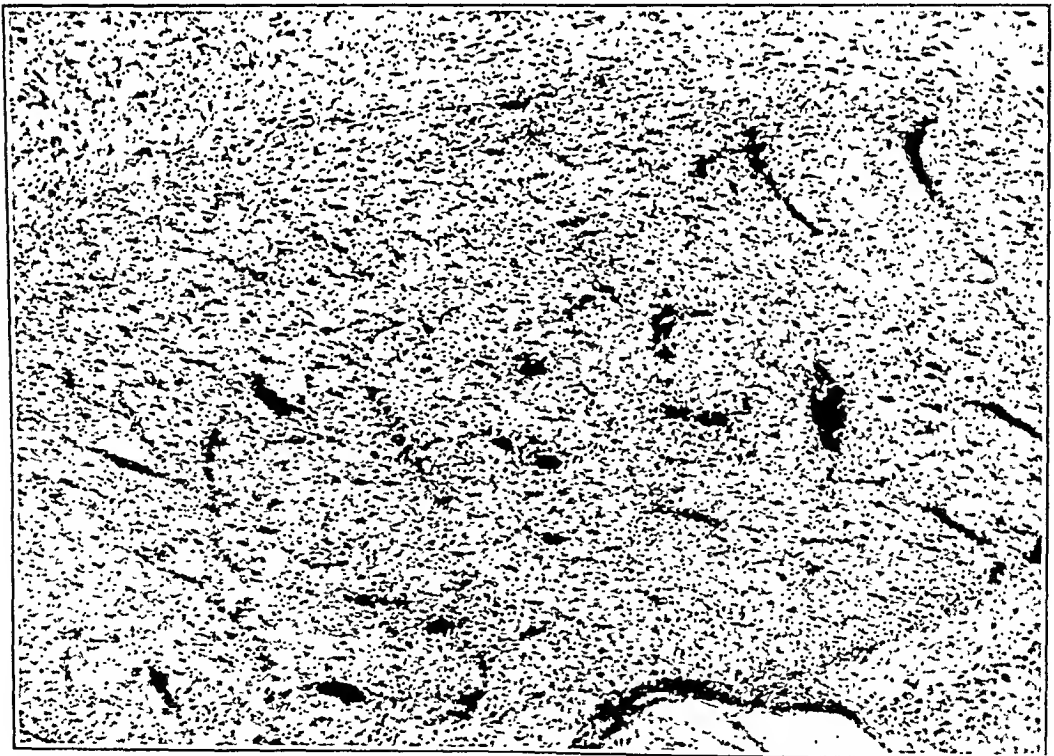


Fig. 10 (rabbit 398).—Multiple foci of perivascular cuffing of hematogenous cells and microglia cells in the peduncle. Nissl stain; $\times 100$.

With respect to destruction of nerve cells as well as of the myelin sheaths, it may be said that disease of the nerve cell bodies was extremely rare. Retrograde degeneration, such as one might expect from involvement of the axons, was not encountered. When inflammatory foci were observed in the gray matter, the nerve cell bodies lying in the midst of the focus could be seen to be unencumbered with reacting cells. By focusing up and down through the lesion, one could clearly see normal-looking nerve cells, unattacked by microglia cells. Neuronal phagia was seen on a few occasions, however. As to the axons, in the early lesions, as in rabbit 487, with a survival time of twenty-one days, they were all apparently normal. In lesions of slightly longer standing,

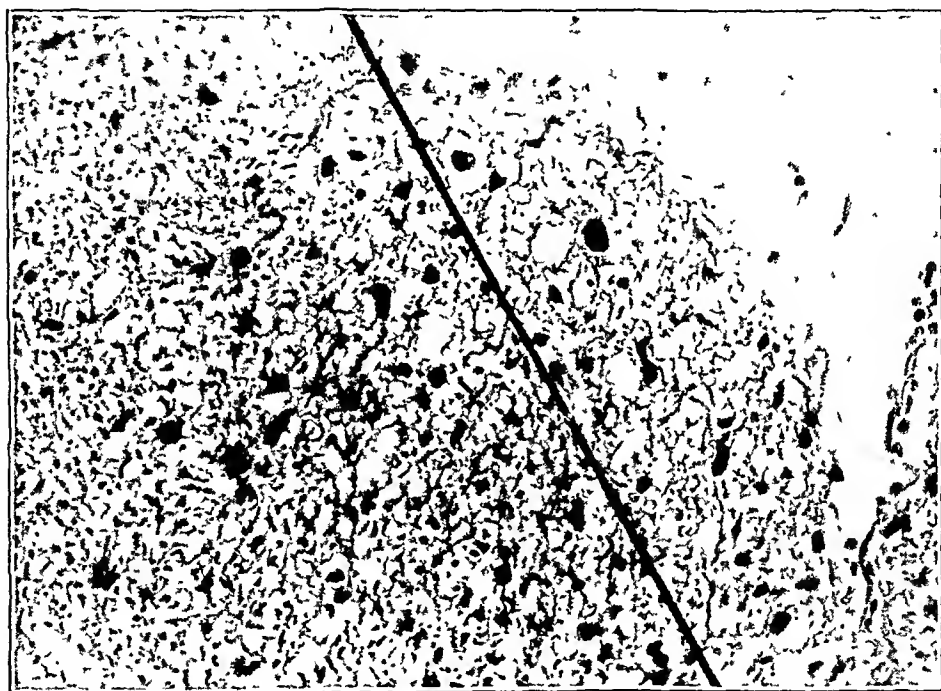


Fig. 11 (rabbit 466).—Loss of axons near the mesial and dorsal edges of the posterior column. The line divides the normal from the pathologic zone, with empty sheath spaces in the latter. Large nuclei of astrocytes are seen. Bodian stain; $\times 400$.

such as those in rabbit 441, with a survival time of fifty-six days, some of the axons were thickened and occasional axons were missing. In older lesions, such as those in rabbit 466, which had a survival time of one hundred and thirty-one days, most of the axons in the affected zone had disappeared, leaving the sheath spaces empty (fig. 11). The greatest loss of axons was in the zone where gliosis had begun to form a fairly dense scar. In the Bodian preparations, scattered among the empty sheath spaces, and in contrast to them, could be seen the large nuclei of astrocytes. The axons in the adjoining zone—separated by

a line drawn across the photograph—appeared normal in size, number and distribution.

All the lesions in any one animal were not of the same age, and they differed in cellular makeup as a consequence. Foci containing lymphocytes and polymorphonuclear leukocytes were assumed to be the youngest lesions; yet sometimes minute perivascular foci composed entirely of microglia cells in the pleomorphic stage were encountered. Here there were no hematogenous cells at all. At any rate, various combinations of hematogenous cells and microglia cells in different degrees of activation, up through gitter cells, were present, as previously described, depending, among other things, on the age of the lesion.

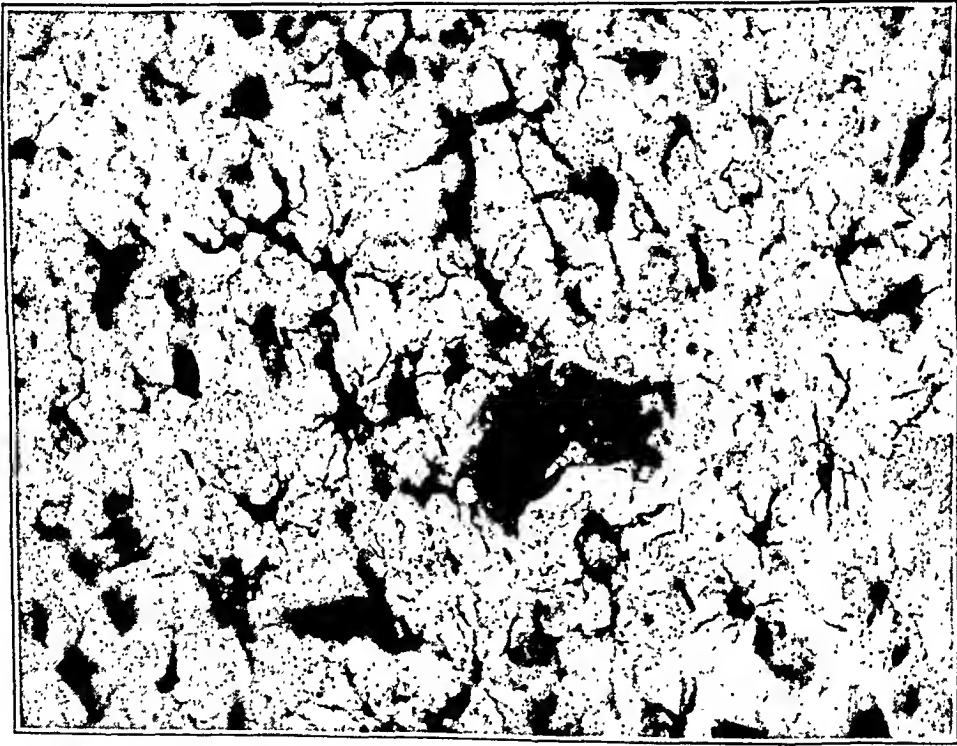


Fig. 12 (rabbit 29).—Focus of perivascular reaction of microglia cells, showing various degrees of activation. Hortege stain; $\times 400$.

But as these foci increased in age astrocytes participated in the reaction. Figure 8 (lower part) illustrates their response. In the spinal cord of animal 463, which had a survival time of four months, fairly dense gliosis could be seen around the edge of the cord in the Cajal gold chloride-mercury bichloride stain. The picture here was not so much a perivascular plaque as it was a deep border around the edge of the posterior column. The scar evidently arose not from the glial processes of the raphe, which was destroyed, but from astrocytes arising in the subpial zone, or growing inward from the healthy tissue beyond the demyelinated region. It will be noticed that the glial scar of figure

8 (lower part) lies in the same part of the section that was seen to be devoid of axons in figure 11.

Holzer preparations showed, in a few instances, early, delicate meshworks of beginning gliosis in the cord or brain, usually perivascular.

COMMENT

The principal histologic features of the lesions in these animals were in general similar from one series to another. Regardless of the details of the technic by which this encephalomyelitis was produced, the main characteristics were similar whether homologous or heterologous antigen was used, or whether homologous antigen was modified by enzyme-substrate activity or augmented by the action of adjuvants. In any case a perivascular reaction of hematogenous and interstitial cells was the rule, followed later by demyelination and fatty degeneration and, in chronic lesions, by astrocytic scar formation. All these characteristics can be observed in cases of multiple sclerosis,⁴ although the infiltration of hematogenous cells, either in the meninges or in the parenchyma, is not a conspicuous feature of the latter disease. This is not necessarily a distinguishing difference, however, as will be mentioned later. As Ferraro⁴ and Putnam²³ have repeatedly maintained, the type of lesion one sees in the various demyelinating diseases depends, to some extent at least, on the age of the pathologic process. Without belaboring this point unduly, it is suggested that there are many features of histologic similarity in the various stages of progress of multiple sclerosis, Schilder's disease, neuromyelitis optica and postinfectious and postvaccinal encephalomyelitis. Further, there is a certain similarity between these demyelinating diseases, on the one hand, and the experimentally produced encephalomyelitis reported in the present study, on the other. It is true that, except for encephalomyelitis postvaccinationem, little clue as to the underlying mechanism is available at the present time, but in the Pasteur treatment for rabies, heterologous antigen capable of inciting the production of antibrain antibodies is introduced. In the other demyelinating diseases no such starting point is known. However, Schwentker and Rivers¹² showed experimentally that homologous brain tissue, after it has been modified by autolysis, also is antigenic, as determined by the complement fixation test. Other methods besides autolysis can be used to denature or modify homologous nerve tissue so that it will become antigenic. In the study reported here it is assumed that the myelin sheath was modified by the action of the enzyme lecithinase and that this resulted in the hydrolysis of lecithin. It is not necessarily implied that hydrolyzing enzymatic activity could

23. Putnam, T. J.: Multiple Sclerosis and "Encephalomyelitis," *Bull. New York Acad. Med.* **19**:301, 1943.

be the underlying mechanism in the production of antigens in some of the demyelinating diseases, but it is interesting in this regard that Brickner²⁴ has reported a demyelinating enzyme in the plasma of patients with multiple sclerosis.

Further consideration of the pathogenesis of the lesions is based on the successful use of killed tubercle bacilli and "bayol F" as adjuvants to enhance the antibody response, in accordance with the technics of Dienes and of Freund, in bringing on clinical and histologic signs of disease of the nervous system. Results with the use of this antigen add to the conviction that the encephalomyelitic reaction is an antibrain-antibody response. The fact that the lesions are perivascular and the reacting cells are lymphocytes and microglia cells is also consistent with an immunologic response. If it is true that antibodies are synthesized in the reticuloendothelial system,²⁵ it is noteworthy that in the central nervous system production of antibodies and phagocytosis are carried out at the same point by the same cells, i.e., perivascularly by histiocytes. If lysis of the myelin sheath is actuated by antibodies derived from the microglia and from lymphocytes, its phagocytosis is carried on by the microglia cells. The cells predominating in these reactions were overwhelmingly microglial, and few, if any, lymphocytes were observed in the parenchymatous tissue, most of them being restricted to the walls of blood vessels, the perivascular space or the subarachnoid space. Whether the microglia was stimulated to hyperplasia by disease of the myelin in the perivascular zones, or whether it was called into activity as a source of antibodies in the zone surrounding blood vessels is, of course, not known. But it was difficult to find even the smallest lesion where microglia cells surrounded the vessel in which the myelin was not already presenting signs of the discoloration or configuration of disease. Like macrophages elsewhere, the microglia cells seemed to respond to injured tissue.

Concerning the blood-brain barrier and the passage of antibodies through it,²⁶ it may be said that this structure must have played some role in these experiments. The antigen, presumably, was not transported from the intradermal sites of inoculation to the brain but had existed in the brain since the earliest days, or at least since the days of maximum myelination, and had no need to cross the barrier, since it was already there. The production of brain-specific antibodies in the brain, especially in the perivascular zone, may, however, have had some functional relation to at least a part of the ectomesodermal

24. Brickner, R. M.: Studies in the Pathogenesis of Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **23**:715 (April) 1930.

25. Dougherty, T. F.; Chase, J. H., and White, A.: The Demonstration of Antibodies in Lymphocytes, *Proc. Soc. Exper. Biol. & Med.* **57**:295, 1944.

26. Friedmann, U.: Blood-Brain Barrier, *Physiol. Rev.* **22**:125, 1942.

barrier. Since lymphocytes are now thought to transport antibodies, the confinement of these cells to the Virchow-Robin space would suggest either the passage through the pia-glia membrane of the antibodies they had been carrying or the transportation of antibodies in the parenchyma by the microglia cells. If all the antibodies were produced in situ by the microglia, it is not clear why the lesions should be perivascular or subpial. Therefore it is probable that at least some of the antibodies involved in these lesions were derived from the perivascular lymphocytes, which in some lesions were seen in abundance; and to be effective, as they were, these antibodies must have passed through, if not the blood-brain barrier, then at least the cerebrospinal fluid-brain barrier. This relation of the site of lesions to the spinal fluid has been pointed out before, especially by Greenfield,²⁷ in writing of postvaccinal encephalomyelitis. It is interesting also to speculate as to whether the meningitis, with its heavy outpouring of lymphocytes, was a source of antibody production in the early days of the disease. At any rate meningitis was seen in the rabbits with the earliest lesions, such as rabbit 464, when practically no microglial reaction had yet started, and then, after reaching a peak in some of the rabbits with longer survival time, cases such as rabbit 487, it subsided, leaving only the parenchymatous lesions of perivascular and subpial microgliacytosis.

Spontaneous encephalomyelitis is a common disease in rabbits, and the possibility of its presence in laboratory rabbits must always be borne in mind. All the animals of this experiment were kept in the same room under about the same conditions. While most of them were kept in individual cages, they had opportunity to come in contact with one another twice a week on inoculation days. If spontaneous encephalitis were enzootic, it is likely that all the animals would have had lesions. Furthermore, the character of the lesions was different in the present series from that described for spontaneous encephalomyelitis.²⁷ While it may be argued that meningitis and perivascular cuffing with hematogenous cells of vessels of the brain could not be distinguished from lesions of spontaneous meningoencephalitis, there were other distinguishing features. Chief among these differences were the hyperplasia of the microglia and the perivascular demyelination and fatty degeneration. In more chronic lesions there was gliosis, as pointed out earlier. Another point of distinction, especially in the series given the tubercle bacillus antigen, was the severity of the lesions of the spinal cord and the appearance of clinical signs within two or three weeks of the inoculation in 9 out of 10 animals. Furthermore, although 3 animals is too small a series to have any statistical significance, the

27. McCartney, J. E.: Brain Lesions of the Domestic Rabbit, *J. Exper. Med.* 39:51, 1924.

series receiving normal cord antigen, in which no lesions could be expected, remained free of lesions.

The reason that 2 of the animals showed pathologic changes without clinical symptoms is not altogether clear, but animal 104 presented only a minimal number of histologic lesions. The lesions were definite enough (fig. 2) but were not plentiful. Many sections had to be examined carefully in order to find them. Also, in the fourth series of rabbits, some animals presented extremely severe neurologic signs, which later practically disappeared; and at least 1 of these rabbits showed little activity histologically but the meninges were slightly thickened. Presumably, most of the symptoms were due to a meningitis which later subsided.

The number of histologic reaction types in the central nervous system is necessarily limited. Such factors as the reacting elements, the time sequence and the circulatory involvement can produce different pathologic pictures in different circumstances, but the types of response, while fairly characteristic, are not numerous. The reaction to virus infection is, with slight modification, the same for one virus as for another. The reaction to bacterial infection differs from the reaction to virus and differs, let us say, from the reaction to infarction. While some diseases, such as tabes dorsalis or pernicious anemia, have loss of the myelin sheath as part of their pathologic picture, they present a histologic picture in no sense to be confused with that seen in the present study. It is interesting, therefore, to point out that the type of reaction associated with multiple sclerosis, Schilder's disease and neuromyelitis optica is similar to that seen in the experimentally produced encephalomyelitis in this investigation, which is based on an immunologic reaction.

SUMMARY

Twenty-one rabbits were inoculated with rabbit spinal cord prepared in four different ways: (1) suspension of normal cord in isotonic solution of sodium chloride, (2) suspension in isotonic solution of sodium chloride of cord in which the lecithin had been hydrolyzed by lecithinase and the lecithinase then removed, (3) a similar suspension with the lecithinase left in, (4) normal cord with the addition of adjuvants "bayol F" and killed tubercle bacilli. Six other rabbits were given injections of human spinal cord treated with solution of formaldehyde U. S. P. Series 4 received but one set of injections. The four other series were given injections repeatedly for varying times, up to about a year.

Series 1 showed no clinical or histologic abnormalities. All the other series presented some cases in which there were clinical signs referable to the central nervous system and extensive histologic evidence

of encephalomyelitis. In the series treated by the adjuvant technic, 9 out of 10 animals were affected. The clinical signs were of the nature of spastic paresis, ataxia, incoordination, generalized weakness and death. The histologic lesions were usually related to blood vessels and consisted of collections of hematogenous cells in the perivascular space and in the meninges and of dense proliferations of microglia cells in the parenchyma of the spinal cord or brain. The disease showed a predilection for the white matter, where demyelination could be observed in lesions of almost any age. In animals with a long survival time early glial scars were seen.

The pathogenesis of the lesions and their possible similarity to the lesions of certain demyelinating diseases are briefly discussed.

Dr. Gardner Middlebrook, of the Rockefeller Institute for Medical Research, New York, furnished the killed tubercle bacilli in "bayol F."

Massachusetts General Hospital.

PSYCHOSURGERY DURING 1936-1946

WALTER FREEMAN, M.D., Ph.D.

AND

JAMES W. WATTS, M.D.

WASHINGTON, D. C.

PSYCHOSURGERY was introduced into this country ten years ago, amid rumblings of disbelief and thunderings of disapproval. It seems appropriate now that a survey of results of the first decade be presented.

It was the experimental work of a group of investigators in Yale University that started Egas Moniz¹ on the surgical treatment of mental disorders. Jacobsen,² in association with Fulton, noted a profound alteration in response to frustration in the chimpanzee with both frontal poles excised. Before operation, if the animal made a few mistakes, he would scream with rage, urinate and defecate in the cage, roll in the feces, shake the bars and refuse to continue the experiments. After the operation the same animal would continue in the experimental situation long beyond the patience of the examiner, making mistake after mistake, without the least indication of being upset emotionally.

At about the same time Brickner³ published an extensive report on the case of a man whose frontal lobes had been removed several years before because of a tumor. This man was of average intelligence, as shown by various tests following the operation, but the striking thing about him was his complete lack of self consciousness and his obliviousness to the seriousness of his own predicament. While Brickner did not mention worry by name, his patient was obviously incapable of exercising this most human of intellectual-emotional exercises.

Egas Moniz had theories of his own, but they tied in well with the findings of Fulton and Jacobsen and of Brickner; therefore he and Almeida Lima commenced operating on psychotic patients and first

Presented at a meeting of the Connecticut State Medical Society, Sept. 10, 1946.

From the Department of Neurology, George Washington University School of Medicine.

1. Egas Moniz: *Tentatives opératoires dans le traitement de certaines psychoses*, Paris, Masson & Cie, 1936.

2. Jacobsen, C. F.: *Studies on Cerebral Function in Primates*, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1936, vol. 13, no. 3.

3. Brickner, R. M.: *Intellectual Functions of the Frontal Lobes*, New York, The Macmillan Company, 1936.

reported their results in the spring of 1936. Fulton called our attention to these reports, and by the end of 1936 we completed our first series of operations on 20 patients.⁴ Seven of these patients had to have a second operation because of relapse, and 2 of them underwent three operations before the psychosis could be overcome. However, a recent check on this first series revealed that 1 patient died after operation and 5 more since, including 1 by suicide. Of the 14 living patients, 4 are employed and 4 are keeping house; 4 are living at home, and only 2 are in institutions (appendix).

At the time of our first reports⁵ we emphasized the need of a long period of observation before definitive conclusions could be drawn. Up to the present time we have kept in touch with all our patients, now numbering well over 400, and the results in succeeding years are on the whole similar to those in the first series. By means of refinements in the technic of prefrontal lobotomy, we are able to secure a higher percentage of successful results in relatively favorable cases; and, knowing what could be accomplished in these, we have undertaken operation in a large number of unfavorable cases. Consequently, the percentages in the various categories of social adequacy have remained about the same over several years.

In prefrontal lobotomy the surgeon incises the white matter in both frontal lobes in such a way as to sever the connections between the thalamus and the frontal pole. From the time of our first operations we have asked ourselves what the operation does to the psychosis to make it clear up. We vividly recall the case of a young woman who was responding with intense fear to her hallucinations. They were of the most disagreeable kind, the voices calling her a dog and threatening her with hell fire. She was in a panic, and her attention could hardly be gained. Within a few hours after operation she described the same experiences but in a subdued tone of voice, as though they were hardly worth mentioning. A few days later, when questioned about the voices, she replied: "Voices? No. My ears have gone dead." This case illustrates the bleaching of the emotional tone and the quieting of anxiety that almost always accompany prefrontal lobotomy. In fact, of all the symptoms of mental disorder, emotional tension has undergone the most profound alteration after prefrontal lobotomy. This does not mean that these patients are apathetic, lacking all emotion. As a matter of fact, as they recover from the post-operative inertia, they are fairly responsive, sometimes more than they were before they became sick; but the emotion attaches itself to external

4. Watts, J. W., and Freeman, W.: *Psychosurgery*, J. Nerv. & Ment. Dis. 88:589, 1938.

5. Freeman, W., and Watts, J. W.: *Prefrontal Lobotomy in the Treatment of Mental Disorders*, South. M. J. 30:23, 1937.

happenings rather than to inner experiences. Patients who have been operated on are usually cheerful, responsive, affectionate and unreserved. They are outspoken, often critical of others and lacking in embarrassment. For the first few weeks or months they are rather childlike in their attitudes and behavior. They require more than the ordinary motivation to accomplish and are satisfied with something less than perfection. They tend to procrastinate, to make up their minds too quickly and to enunciate opinions without considering the various implications. Some patients are distractible, others have single track minds; some are indolent, others are human dynamos. The most striking and constant change from the preoperative personality lies in a certain unselfconsciousness, and this applies both to the patient's own body and to his total self as a social unit. The patient emerges from operation with an immature personality that is at first poorly equipped for maintaining him in a competitive society; but with the passage of time there is progressive improvement, so that in about one-half the cases earning a living again becomes possible.

On the basis of these experiences, we have advanced the hypothesis⁶ that the frontal lobes are especially concerned with foresight and insight and that the emotional component associated with these functions is supplied by the thalamus. When the thalamic connections are severed, the functions of foresight and insight suffer temporary obliteration, and even in the later course of recovery are never as completely endowed with feeling tone as they were before. A modicum of function is preserved, because the direct connections are not completely severed and because indirect connections probably also exist. Foresight and insight are two very important functions for any person living in a complex society. One may well ask whether the surgeon is justified in depriving a patient of these functions even for the sake of relieving his psychosis. We believe that the surgeon would be entirely justified if it could be shown that the patient became psychotic because of perversions of these same functions of foresight and insight, together with the attachment of an abnormal emotional tone.

When one studies a psychotic patient with these functions in mind, it is not so difficult, if the case is not far advanced, to determine the fact that many of the symptoms of the psychosis may indeed be attributed to pathologic selfconsciousness. Why otherwise would a patient believe that *he* was being kept under surveillance by the F.B.I.; that German spies were entering *his* room, using thought control on *him*, putting dope

6. Freeman, W., and Watts, J. W.: Interpretation of the Functions of the Frontal Lobes Based upon Observations in Forty-Eight Cases of Prefrontal Lobotomy, Yale J. Biol. & Med. 11:527, 1939; Psychosurgery, Springfield, Ill., Charles C Thomas, Publishers, 1942.

in *his* food or accusing *him* of sexual perversions? These ideas are intensely personal to him and preoccupy his mind to the exclusion of all rational, coherent thought processes. Or take a patient who has a string of complaints as long as his arm concerning *his* stomach and *his* bowels, *his* heart and *his* head. Here is a person, also, whose function of consciousness of the self has gone beyond normal limits into a state of hypochondriasis. His attention becomes concentrated on his various organs to the exclusion of everything else. In both cases there is also a distressing concern for the future; not only what "they" are going to do to him, but also in regard to the prospects of the ulcer, cancer or heart trouble. Above all, there is the emotional component which invests the symptoms and the ideas with a disabling force and completely prevents the patient's adaptation to the realities of existence. Such persons are *sentient* rather than *rational beings*. They live with their emotion concentrated on themselves, with an admixture of self pity or guilt that induces invalidism or, at the last extremity, suicide.

Prefrontal lobotomy cuts off the emotional component concerned with these ideas. It relieves the symptom of mental pain. In temporarily abolishing foresight and insight, the operation breaks the vicious circle of preoccupation, emotional tension and imagination that makes the suspected disease or persecution much more serious than any reality could be. It brings the patient back to earth and the enjoyments thereof.

The past decade has seen a certain vindication of our ideas on the subject of prefrontal lobotomy. Even in our first papers we cautioned against going to extremes. Now, at the beginning of the second decade, we would reiterate these cautions. Prefrontal lobotomy is an operation of last resort. It should be performed only on those patients who no longer have a reasonable hope of spontaneous recovery. It should be done only in cases of threatened disability or suicide, and only after conservative measures have failed. It should be done with the full appreciation of the changes in personality that will inevitably be brought about in the patient if the operation is to succeed, and with a knowledge of possible unfavorable results, such as persistent inertia, convulsive seizures, incontinence and aggressive misbehavior. At the same time, prefrontal lobotomy should be performed while the patient is still fighting his disease, in other words, while the emotional tension is still present to a considerable degree. When emotion subsides and the patient accepts his dream world in lieu of reality, surrenders to his fantasies, then there is little that surgery can accomplish. It has been suggested that if a patient with dementia precox fails to improve after a year prefrontal lobotomy should be considered. In view of the poor prognosis of dementia precox, we should be inclined to accept this idea. In our cases in which operation was performed within the first two years of illness the

percentage of good results was 85, whereas of those cases in which operation was done after two to thirty years of illness good results were obtained in only 31 per cent.⁷

The types of patients who respond best to prefrontal lobotomy are those with the obsession-tension states, with or without compulsions, and the chronic anxiety syndromes, with or without hysterical conversion. Twenty years of invalidism can vanish in a few weeks. Involutional depressions also clear up in a goodly percentage. Schizophrenic states are strikingly modified if the patient is excited, resistive, assaultive and disturbed. The quiet, deteriorated patients are usually unchanged. Alcoholic, psychopathic and epileptic patients, criminals and patients with organic diseases of the brain are seldom benefited.

Prefrontal lobotomy is being adopted in many parts of the world. The war interfered with the development of the procedure in continental Europe, so that the United States and Great Britain got a head start, especially so far as detailed studies are concerned. Portugal and Italy, which had been in the forefront, dropped behind. Scattered reports have come from various Latin American republics; from Sweden and Czechoslovakia; from India, New Zealand and Hawaii. More enthusiasm seems to be present in England than anywhere else. McKissock stated in April 1946 that he had personally performed 500 operations, and in the June 1946 issue of the *Proceedings of the Royal Society of Medicine* there are statistics on more than 800 cases.⁸ In this country, we should estimate that up to the present time approximately 2,000 lobotomies have been performed. A recent survey by Brody and Moore⁹ called attention to the rather great similarity of reports from various clinics in the percentage of patients who derive benefit from the operation. In round figures, one-third recover, one-third improve and one-third fail to improve. There are variations from one investigator to another and from one disease to another, but the results are sufficiently good to warrant the use of prefrontal lobotomy on a large scale for the relief of the very serious and chronic forms of mental disease that keep the back wards of the psychiatric hospitals filled to capacity and beyond.

We would close this review of prefrontal lobotomy by calling attention to its use in the treatment of pain due to organic disease. In case of an incurable illness, such as cancer, or of persistent pain in a phantom limb, intractable causalgia or the lightning pains of arrested tabes, the physician is likely to give up too easily and to prescribe narcotics, to

7. Watts, J. W., and Freeman, W.: Prefrontal Lobotomy: Factors Influencing the Prognosis, *J. South. Med. & Surg.* **108**:242, 1946.

8. Discussion on Prefrontal Leucotomy with Reference to Indications and Results, *Proc. Roy. Soc. Med.* **39**:443 (June) 1946.

9. Brody, E. B., and Moore, B. E.: Prefrontal Lobotomy: A Review of Recent Literature, *Connecticut M. J.* **10**:409, 1946.

the ultimate detriment of the patient with long-standing illness. A year ago we reported experiences in the relief of long-standing pain with prefrontal lobotomy.¹⁰ It would seem that in cases of this condition, as in the cases of purely mental disorders, it is the emotional component, the consciousness of the part and the anticipation of the future disability and death that contribute to the distress of the patient. In many cases the attitude of the patient toward his disease is more disabling than the disease itself; the fear of pain, greater than the pain. With prefrontal lobotomy the physician now has it in his power to relieve the fear, the anticipation, and to render the illness more tolerable to the patient. Since this can be done without significant impairment of intellectual capacity, it would seem that prefrontal lobotomy might be a very considerable boon to the large number of patients whose life will not be long but will, nevertheless, be made miserable by suffering. The physician cannot be criticized for recommending prefrontal lobotomy in order to secure a certain euphoria for those patients who have only pain and death to look forward to.

APPENDIX

The 20 cases in which operation was performed in 1936 were reported in 1938.¹¹ A brief follow-up report as of September 1946, approximately ten years after the first lobotomy, is now given. All the patients have been kept under rather close observation at intervals of a year or less. The same case numbers are used.

CASE 1.—A housewife aged 63 had a history of agitated depression of one year's duration, with two previous nervous breakdowns. After prefrontal lobotomy she quieted down, went out socially, drove her car, kept the household accounts, enjoyed her home but took little responsibility. She had several epileptic seizures, fracturing her wrist in one of them. In 1941 she died of pneumonia. Her husband wrote that the last five years were the happiest of her life.

CASE 2.—A woman aged 59, a bookkeeper, had agitated depression of six months' duration, probably complicated by intoxication with sedatives. Prompt recovery followed prefrontal lobotomy, with return to work in three months. She continued this work for eight years, until her retirement because of age, and then returned to her office to help out during the war. She finally retired in June 1946 and has been living comfortably at home.

CASE 3.—A housewife aged 34 had obsessive preoccupation, depression and suicidal ideas of three years' duration. The first lobotomy was performed in December 1936, with little improvement; the second, in September 1937, with no change, and the third, in 1941, with extreme flattening of emotional life. She presents extreme indolence, petulance and puerility and assumes no responsibility for the care of the home. She presents a rather pleasant front but has a sterile intellectual life. She is cared for at home by her mother.

10. Freeman, W., and Watts, J. W.: Pain of Organic Disease Relieved by Prefrontal Lobotomy, *Lancet* 1:953, 1946.

11. Watts, J. W., and Freeman, W.: Psychosurgery, *J. Nerv. & Ment. Dis.* 88:589 (Nov.) 1938.

CASE 4.—A housewife aged 49 had involutional depression of one year's duration (with a history of three previous attacks) and organic changes caused by a nearly successful suicidal attempt with gas. After lobotomy she continued to show apathy, loss of memory and other signs of organic disease of the brain. She had frequent convulsions and incontinence. She died in status epilepticus in 1944. Autopsy showed minimal operative lesions (all lobotomies in 1936 were done by the Egas Moniz "core" technic), but there were extensive cortical softening at the base of the frontal and temporal lobes and necrosis of the globus pallidus.

CASE 5.—A housewife aged 35 had a history of depression and agitation of four years' duration and three suicidal attempts. She benefited only temporarily from the operation, failed to make a satisfactory adjustment at home or on the farm and finally committed suicide in 1940. Autopsy was not performed.

CASE 6.—A housewife aged 60, with agitated depression, died on the sixth post-operative day of hemorrhage. Autopsy was not performed.

CASE 7.—A business man aged 59, with a history of involutional depression of nine years' duration, improved briefly after lobotomy but relapsed before he could return to his office. A second lobotomy was undertaken by a different surgeon in 1938, and the patient emerged permanently relieved of his depression but with a boisterous, arrogant and extravagant nature that required institutionalization. His condition remains unchanged, after eight years.

CASE 8.—A housewife aged 62 had a history of hypochondriasis of seventeen years' duration with superimposed agitated depression for two years. A year after operation she found part-time employment as a practical nurse and continued in this work until 1945, when she went to live with her daughter. She is fat, jolly and outspoken and is said to be "quite a worker for her age." The visceral complaints cleared up.

CASE 9.—A housewife aged 48, with involutional depression of two years' duration, had had many admissions to the hospital for abdominal complaints. No improvement followed the first lobotomy, in November 1936. The second operation was performed in March 1937, with relief. However, the patient was indolent and sarcastic and was subject to outbursts of anger, which made it necessary to confine her in an institution for eighteen months. After this she resumed her household duties, cared for her grandchildren during the war and still performs most of the domestic work in her daughter's home. On several occasions she has had fleeting depressions, only one of which was sufficiently severe to require treatment; two electroshocks were sufficient.

CASE 10.—A housewife aged 60, with agitated depression of seven years' duration, had transitory improvement after the first lobotomy, in November 1936. At the second operation, in March 1937, severe bleeding was encountered, and the operation was not completed. The patient remained unimproved and died of a heart attack the following July. Autopsy was not performed.

CASE 11.—A secretary aged 32, with catatonic schizophrenia of two months' duration and a history of a previous attack in 1934, lasting only a month, recovered rapidly, and apparently completely, after lobotomy and returned to her position. She was unable to continue because of return of emotional tension, followed by another catatonic attack, for which she was hospitalized in July 1937. Insulin and metrazol shock treatments failed to induce recovery; her family refused permission for further operation, and she remains in the hospital, greatly deteriorated, fat and inaccessible.

CASE 12.—A stenographer aged 25 entered a catatonic state in July 1936 and showed no change after unilateral prefrontal lobotomy. When operation was performed on the opposite side, she "woke on the table." She improved slowly; in a year she took a course in interior decorating but did nothing constructive with it, then returned to work as a stenographer and continued in this until 1942, when she again lapsed into a catatonic state. More extensive prefrontal lobotomy again abolished the condition, but she made a slow and imperfect recovery and was rather hostile to her family. After two years she found a clerical position and a separate domicile and continued living in this way for over a year; but when her parents became ill she returned home and has cared for them in small ways for the past year.

CASE 13.—A cement finisher aged 33 had obsessive preoccupation with his heart and general exhaustion of eighteen months' duration. After prefrontal lobotomy he was euphoric but soon relapsed. Two years later, however, he was able to resume laboring work part time. His adjustment improved with time, and for the past four years he has been steadily employed as janitor at a school, where he is highly thought of.

CASE 14.—A housewife aged 30 had agitation, feelings of unreality and probably hallucinations of six years' duration. After prefrontal lobotomy she made an erratic adjustment and was in and out of hospitals for four years. After that she was divorced, and since remarried and writes enthusiastically of her new life.

CASE 15.—A stenographer aged 42 had an acute onset of catatonic stupor in the course of rheumatic heart disease of many years' duration. Both the mental symptoms and the cardiac irregularity cleared up briefly after prefrontal lobotomy, but the improvement was not sustained. She died of congestive heart failure in April 1937 with recrudescence of mental symptoms.

CASE 16.—A housewife aged 60 had a history of obsessive-compulsive neurosis dating back thirty-six years, with intervals of good health, but with complete disability of four years' duration. Prefrontal lobotomy was followed by temporary euphoria and later return of symptoms. The second lobotomy, in March 1937, was followed by immediate disappearance of the emotional toning, but with persistence of the compulsive washing and brushing for at least three years. She presented marked increase in weight and was outspoken, tactless and disagreeable with her family. There has been steady improvement over the years, although she still shakes her skirts at imaginary dirt. She recently celebrated her seventieth birthday, and is cheerful, outspoken and rolipoly.

CASE 17.—A telephone operator aged 33, with obsessive syphilophobia of twelve years' duration, obtained partial relief from operation and was able to return to work. After a broken engagement her fears returned, and a second lobotomy was performed in 1938. She immediately lost her fears but became indolent and talkative in a silly, vapid way, was too distractible to continue at her work, helped out on a farm for a year or two and for the past two years has been steadily employed in a mill. She writes in a rather childish way of her plans for getting married.

CASE 18.—An attorney aged 37 had a history of severe psychoneurosis complicated with alcoholism of many years' duration. Prefrontal lobotomy relieved his fears but not his alcoholism, and he made an erratic adjustment for several years, enlisting in the Army and serving with the military police until his active service was terminated, after the third court-martial, with a psychiatric discharge. Since then he has been performing legal work for the Government, with incessantly less frequent alcoholic bouts.

CASE 19.—A bookbinder aged 40 had been hypochondriacal since girlhood, with a record of twelve to eighteen abdominal operations. She had been bedridden for two years. She walked on the third postoperative day and thereafter recovered slowly, but surely. She has been employed for the past seven years at her old job. She still complains when asked about her symptoms but never mentions them otherwise.

CASE 20.—A housewife aged 40, with attacks of manic-depressive psychosis at long intervals, recovered in about a year from an episode in 1929 and was free for seven years. During the attack in 1936 she attempted suicide, sustained severe internal injuries but had only fleeting relief from depression. Prefrontal lobotomy was carried out in December 1936, with fleeting improvement. The following spring she again attempted suicide and sustained extensive burns. The clinical picture was decidedly schizoid at that time, and she was maintained in a psychiatric hospital for over a year. Finally, she received a brief course of metrazol shock therapy and recovered promptly. She has been taking care of her household satisfactorily for the past five years in spite of major domestic difficulties.

2014 R Street, N. W.

PENICILLIN IN TREATMENT OF NEUROSYPHILIS

BERNHARD DATTFNER, M.D.

SAMUEL S. KAUFMAN, M.D.

AND

EVAN W. THOMAS, M.D.

NEW YORK

THE PROPER evaluation of success in treatment of neurosyphilis has always been a problem. When Wagner-Jauregg reported the beneficial effect of malaria in treatment of dementia paralytica twenty-seven years ago, there were no objective criteria to prove his point other than clinical improvement. Since spontaneous remissions are common in dementia paralytica, most authorities insisted on an extended period of observation before accepting malaria as a therapeutic agent. A few years later it became obvious that fever therapy, unlike any previous form of treatment, at least prolonged the life span of the patient with dementia paralytica. However, it still remained uncertain whether the therapeutic success would be permanently maintained, i. e., whether the disease process had been definitely arrested. To this the clinical follow-up of the patient failed to give an adequate clue. As time went on, it was found that reversible and irreversible signs and symptoms could exist side by side in neurosyphilis and that the improvement of symptoms in some instances might be only transitory and misleading so far as the activity of the syphilitic infection was concerned. It also became increasingly evident that signs and symptoms might persist or become even more prominent although the specific process in the central nervous system had been completely checked, as proved by the fact that further antisymphilitic therapy was of no benefit. Finally, it was found that the syphilitic infection might be very active within the central nervous system and yet produce no signs or symptoms. Such activity was determined by means of changes in the spinal fluid.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the New York University College of Medicine.

From the Departments of Medicine, Dermatology and Syphilology, and Neurology, New York University College of Medicine; and the Departments of Medicine, Dermatology and Syphilology, Third Medical Division (New York University), and Neurology, Second Medical Division (Cornell), Bellevue Hospital.

Consequently, attention was turned to study of the changes in the spinal fluid. As early as 1924 the observation was made¹ that proper evaluation of the spinal fluid syndrome, with special emphasis on the cell count, enabled one to forecast with considerable accuracy the degree of activity of the syphilitic infection in the central nervous system. The criteria for determining activity have been given in previous papers.² In spite of these observations, the efficacy of treatment of neurosyphilis continues to be evaluated by some almost entirely on the basis of clinical improvement. We believe that this is a serious mistake. Little or no improvement can be expected in cases of neurosyphilis in which there has been widespread destruction of nerve tissue, as in cases of far advanced tabes dorsalis and dementia paralytica. One should never forget that antisymphilitic treatment is directed solely against the invading spirochetes and has no effect on diseased tissue except to remove the cause of the disease. Damaged nerve tissue may or may not recover function after the removal of the infection, depending on the degree and site of the damage. Because of this obvious and irrefutable fact, the spinal fluid syndrome affords the best guide to the activity of a syphilitic infection of the central nervous system and to the effect of treatment. Observations on hundreds of patients carried on over a period of years have proved the validity of this statement.³

A proper evaluation of the spinal fluid findings requires (1) a cell count, (2) determination of the total protein content, (3) a specific test for syphilis and (4) the colloidal gold test. The cell count affords the most valuable information as to the activity of the syphilitic infection in the central nervous system. A cell count of more than 4 per cubic millimeter is evidence of an active process. This belief is based on our own experience at Bellevue Hospital, where each year we make from 3,000 to 4,000 examinations of the spinal fluid, and on the reports of other investigators in this field.⁴ An increase in total protein may

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2. (a) Dattner, B., and Thomas, E. W.: The Management of Neurosyphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:21, 1942. (b) Dattner, B.; Thomas, E. W., and Wexler, G.: Rapid Treatment of Neurosyphilis with Malaria and Chemotherapy, *ibid.* **28**:265, 1944.

3. Dattner, B.: The Management of Neurosyphilis, New York, Grune & Stratton, Inc., 1944.

4. Neel, A. V.: The Content of Cells and Protein in the Normal Cerebrospinal Fluid, Copenhagen, Ejnar Munksgaards Forlag, 1939. Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940. Boyd, W. R.: The Cells in the Cerebrospinal Fluid, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932. Greenfield, J. G., and Carmichael, E. A.: The Cerebrospinal Fluid in Clinical

indicate activity of the infection, as may the colloidal gold tests. The Wassermann test determines the specificity of the process.

We have found that after successful fever therapy the first of the abnormalities of the spinal fluid to become normal is the cell count. The protein values, the readings in the colloidal gold test and the titers in quantitative Wassermann tests decrease gradually, usually in the order given. In some cases five or more years passed before the Wassermann reaction became completely negative. That the Wassermann reaction of the spinal fluid does become negative within a few years after the completion of successful treatment in many cases is proved by the records of patients treated in Wagner-Jauregg's clinic in Vienna,³ some of whom were under observation for more than fifteen years; our own experience with malaria therapy at Bellevue Hospital, and that of other investigators.⁵

The purpose of this paper is to report our experience with penicillin in the treatment of neurosyphilis. The foregoing introduction seemed necessary, since the most objective criteria are essential in the evaluation of any therapy. We believe the spinal fluid findings, with few exceptions, afford reliable objective data in the management of neurosyphilis.

METHODS USED IN EXAMINATIONS OF THE SPINAL FLUID

Cell counts were made in the Fuchs-Rosenthal chamber, which holds 3 cu. mm. Therefore, we shall report our cell counts in thirds. The counting of 3 cu. mm. reduces the margin of error.

Quantitative protein estimations were made by a sulfosalicylic acid method, using an electrophotometer which gives reproducible readings. Values of 30 mg. per hundred cubic centimeters are regarded as the upper limit of normal.

Cell counts and total protein determinations were made both in our own laboratory and in the laboratory of the New York City Branch of the New York State Department of Health. There was excellent agreement between the findings of the two laboratories.

Diagnosis, London, Macmillan & Company, Ltd., 1925. Merritt, H. H., and Fremont-Smith, F.: *The Cerebrospinal Fluid*, Philadelphia, W. B. Saunders Company, 1938. Fuchs, A., and Rosenthal, R.: *Physikalisch-chemische, zytologische und anderweitige Untersuchungen der Zerebrospinalflüssigkeit*, Wien. med. Presse **45**:2082, 2190 and 2242, 1904. Eskuchen, K.: *Liquoruntersuchung*, Neue deutsche Klin. **6**:213, 1930. Lange, C., and Harris, A. H.: *Interpretation of Findings in the Cerebrospinal Fluid*, Arch. Neurol. & Psychiat. **53**:116 (Feb.) 1945.

5. O'Leary, P. A., and Brunsting, L. A.: *The Non-Specific Treatment of Neurosyphilis*, J. A. M. A. **94**:452 (Feb. 15) 1930. Plaut, F.: *Klinische Verwertung der Liquoruntersuchung vom Standpunkt des Neurologen*, in Jadassohn, J.: *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1929, vol. 17, p. 568. Hinsey, L. E., and Blalock, J. R.: *Treatment of General Paralysis: Results in One Hundred and Ninety-Seven Cases Treated from 1923 to 1926*, Am. J. Psychiat. **11**:541, 1931.

The quantitative complement fixation tests of the spinal fluid and the colloidal gold tests were made by the laboratory of the New York City Branch of the New York State Department of Health, through the courtesy of Dr. Edgar R. Maillard.

The complement fixation tests were titered in exactly the same manner as the complement fixation tests of the blood. This measurement of the reagin in the spinal fluid has proved much more satisfactory than the older method of doing complement fixation tests on varying amounts of spinal fluid.

The colloidal gold tests were made by the new Lange⁶ method, which employs a sensitive gold sol made by the reduction of gold chloride with sodium citrate, a buffered solution being used as diluent. The reactions obtained with each of ten dilutions of cerebrospinal fluid are compared with a color standard ranging from 0 to 20. The numerical values are added to yield the total. This has the advantage of furnishing a quantitative as well as qualitative test. The sum of the reactions in all ten tubes in normal fluids should not be over 50. The highest possible reading in abnormal fluids would be 200. For purposes of tabulating colloidal gold curves in the tables of this report, we have chosen to give the first four figures of the older conventional colloidal gold curve when that test was used at the beginning of our survey. Since the introduction of the new Lange colloidal gold test, we report the total figure obtained by adding the numerical values in all ten tubes.

SELECTION OF PATIENTS

To eliminate variables in our experiments, we chose for treatment with penicillin only patients with "active spinal fluids," and all the patients in the series had syphilis of more than two years' duration. By the term "active spinal fluid" we mean a fluid which gives a positive reaction in the complement fixation tests for syphilis and contains more than 4 cells per cubic millimeter. The cell counts of the spinal fluids of this series of patients prior to treatment with penicillin varied from a maximum of 1,540 cells to a minimum of 16 per 3 cu. mm. In our experience we have encountered few, if any, untreated patients with active neurosyphilis who had normal cell counts of the spinal fluid.

Determinations of the total protein content of the spinal fluid of patients in this series prior to treatment varied from a maximum of 188 mg. to a low of 19 mg. per hundred cubic centimeters, only 6 patients having had below 25 mg. per hundred cubic centimeters. The highest protein values, as a rule, were found in patients with dementia paralytica.

Complement fixation titers prior to treatment varied from a maximum of 530 units to a minimum of 4 units. Only 6 patients had complement fixation titers below 10 units. There was no relation between the height of the complement fixation titer and the severity of the signs and symptoms.

First zone colloidal gold curves were reported for practically all the patients with dementia paralytica, the highest total reading having been 190. First zone colloidal gold curves with high total readings were also found for many patients with diseases diagnosed as asymptomatic neurosyphilis, meningovascular syphilis and tabes dorsalis.

EVALUATION OF PENICILLIN IN TREATMENT OF NEUROSYPHILIS

Examinations of the spinal fluid were made immediately before treatment with penicillin and at three month intervals thereafter for the first twelve to eighteen

6. Lange, C.: Methods for the Examination of Spinal Fluid, Am. J. Syph., Gonorr. & Ven. Dis. 23:638, 1939.

months and then every six months. In addition, patients were checked every month with titrated complement fixation tests of the blood. While we deliberately relied primarily on the laboratory data as our guide to treatment, clinical manifestations were by no means ignored. Every patient was thoroughly examined before treatment and at regular intervals thereafter. We are well aware that from the point of view of public health, as well as that of the patient, the final goal in therapy is normal function or the regaining of as much function as possible. The desire to renew proper function, however, cannot serve as the primary factor in a scientific evaluation of the effect of treatment in arresting or eliminating an infection.

Further to reduce the variables, we used penicillin exclusively and administered it to all patients intramuscularly in individual doses dissolved in water at three hour intervals. The only variants were the number of injections and the amount of penicillin given in different groups. The total dose varied from 2,000,000 to 9,000,000 Oxford units, only 1 patient having received 9,000,000 units. The number of injections varied from seventy-five to two hundred. No patient received intrathecal therapy, and no additional treatment with other drugs was given during or after administration of penicillin.

Because of the shortage of penicillin early in the course of the study, we originally treated numerous patients having no or mild symptoms with as little as 2,000,000 units. For the past ten months we have adopted a schedule calling for individual injections of 40,000 units of penicillin every three hours for one hundred and fifty doses, making a total of 6,000,000 units for all patients with "active spinal fluids," regardless of the symptoms and signs. In our experience, it is not true that patients with late asymptomatic neurosyphilis require less treatment than patients with other forms of neurosyphilis.

One hundred and fifty-one patients treated with penicillin were followed with clinical examinations and studies of the spinal fluid for six months or more after treatment. The longest period of observation was twenty-eight months. We chose six months as the minimum period of observation because with malaria therapy we found that less than 2 per cent of the patients with normal cell counts of the spinal fluid six months after treatment relapsed at a later period. The percentage of relapses after six months of follow-up observation among patients treated with the smaller amounts of penicillin was slightly higher than that after malaria therapy. Consequently, in reporting on patients observed for only six months after treatment, we recognize the possibility that some of them may relapse at a later period.

In tabulating statistics, we included among patients considered to show a satisfactory response all those who had normal cell counts of the spinal fluid and satisfactory improvement in other spinal fluid findings, i.e., definite decreases in titer in complement fixation tests and in the total protein values, as well as improvement in the colloidal gold curves. All but 8 of the patients included in the group showing satisfactory response to treatment had transitional abnormalities in the spinal fluid in that the reactions to the complement fixation tests and the colloidal gold tests were still abnormal. The spinal fluids of the 8 exceptional patients became completely normal between nine and twenty-four months after treatment. For some of the patients with transitional abnormalities of the spinal fluid the total protein is not entirely normal at the time of writing.

Among the patients representing therapeutic failures after the original course of penicillin therapy were included all those who did not have a normal cell count of the spinal fluid six months after therapy or who relapsed at some later period. All but 3 were again treated. These 3 patients have been notified to return to the hospital for retreatment.

Table 1 gives the status of 151 patients on the basis of their original treatment. Table 2 shows the management and disposition of the 20 patients who did not respond satisfactorily to the original treatment. Table 3 gives the present status of 151 patients, including the results of treatment.

TABLE 1.—*Results of First Course of Treatment in One Hundred and Fifty-One Cases of Neurosyphilis*

Type of Neurosyphilis	Total Number of Patients	Satisfactory Response	Failure	Patients Retreated After Therapeutic Failure
Asymptomatic.....	23	17	6	5
Meningovascular.....	35	28	7	5
Tabes dorsalis.....	41	37	4	4
Dementia paralytica.....	33	30	3	3
Tabetic form of dementia paralytica.	19	19	0	0
Total.....	151	131 (67%)	20 (13%)	17

TABLE 2.—*Analysis of Unsatisfactory Results After First Course of Penicillin Treatment*

Case No.	Type of Neurosyphilis	Original Dose, Million Units	Retreat-ment Dose, Million Units	Present Status
1.....	Asymptomatic	2	8	Satisfactory *
2.....	Asymptomatic	2	8	Satisfactory *
3.....	Asymptomatic	2	6	Indefinite †
4.....	Asymptomatic	3	8	Indefinite †
5.....	Asymptomatic	2	6	Indefinite †
6.....	Asymptomatic	2	None	Failure ‡
7.....	Meningovascular	3	8	Satisfactory *
8.....	Meningovascular	4	8	Indefinite †
9.....	Meningovascular	3	8	Indefinite †
10.....	Meningovascular	4	8	Indefinite †
11.....	Meningovascular	2	8	Indefinite †
12.....	Meningovascular	6	None	Failure ‡
13.....	Meningovascular	2	None	Failure ‡
14.....	Tabes dorsalis	4	5	Failure (patient died);
15.....	Tabes dorsalis	2	6	Indefinite †
16.....	Tabes dorsalis	2	8	Indefinite †
17.....	Tabes dorsalis	4.5	8	Indefinite †
18.....	Dementia paralytica	5	8	Satisfactory *
19.....	Dementia paralytica	5	8	Indefinite †
20.....	Dementia paralytica	6	8	Indefinite †

* Patient followed for six or more months after retreatment.

† Present status indefinite because of inadequate follow-up period after retreatment or because of a borderline spinal fluid syndrome.

‡ Patient needs retreatment.

The patients who were retreated and whose spinal fluid findings are now satisfactory are included with the patients whose response is considered satisfactory: Seventeen were retreated. Four of these are listed in the group showing a satisfactory response, for a follow-up period of six months or more shows a satisfactory transitional spinal fluid spectrum. A greatly debilitated patient with tabes dorsalis died, although he had received two courses of penicillin, three months apart.

of 4,000,000 and 5,000,000 units, respectively. The 12 other patients were listed in the group with an indefinite status because the period of observation had not yet been sufficient or because the spinal fluid syndrome was borderline. For none of these 12 patients, however, can the result be classified as a failure at the time of this report. Of the 20 patients whose responses were considered unsatisfactory after the first course of treatment, 12 originally received only 2,000,000 or 3,000,000 units of penicillin, an amount which we now regard as inadequate.

TABLE 3.—*Present Status of One Hundred and Fifty-One Patients Treated for Neurosyphilis, Including Those Retreated*

Diagnosis	Total No. of Patients	Satisfactory	Indefinite	Failure
Asymptomatic neurosyphilis.....	23	19	3	1
Meningovascular syphilis.....	35	29	4	2
Tabes dorsalis.....	41	37	3	1
Dementia paralytica.....	33	31	2	0
Tabetic form of dementia paralytica.....	19	19	0	0
Total.....	151	135 (90%)	12 (7%)	4 (3%)

TABLE 4.—*Dose of Penicillin in First Course of Treatment of Neurosyphilis*

Diagnosis	Total No. of Patients	Dose, Millions of Oxford Units					
		2	3	4	5	6	9
Asymptomatic neurosyphilis.....	23	15	1	6	0	1	0
Meningovascular syphilis.....	35	5	8	13	0	9	0
Tabes dorsalis.....	41	4	21	9	1	6	0
Dementia paralytica.....	33	0	0	23	5	4	1
Tabetic form of dementia paralytica.....	19	0	1	15	0	3	0
Total.....	151	24	31	66	6	23	1

In addition to the patients whose response to the first course of penicillin was regarded as an unquestionable failure 6 patients with normal cell counts six months after the original course of penicillin therapy were treated again because of our desire to see whether further clinical improvement could be achieved with additional penicillin therapy. The results of treatment of these patients did not convince us that additional treatment with penicillin resulted in further improvement of function.

Table 4 gives the dose of penicillin originally given to patients classified according to the involvement of the central nervous system.

Table 5 gives the length of follow-up observations on 135 patients classified as giving a satisfactory response to treatment. Of this group, 100 were observed from twelve to twenty-eight months. Most of them still have transitional abnormal spinal fluid findings, but we believe that

in the course of time they will have completely normal fluids, as indicated by the continuous and persistent trend toward normality in all the spinal fluid findings. From past experience with fever therapy, we have good reason to believe that further treatment with either peni-

TABLE 5.—*Period of Observations of Follow-Up on Patients with Satisfactory Response to Treatment for Neurosyphilis*

Diagnosis	Total No. of Patients	Period, Months				
		6	9	12	18	24 or More
Asymptomatic neurosyphilis.....	19	1	0	9	8	1
Meningovascular syphilis.....	29	6	8	8	2	5
Tabes dorsalis.....	37	6	4	8	11	8
Dementia paralytica.....	31	5	1	13	5	7
Tabetic form of dementia paralytica.....	19	2	2	4	7	4
Total.....	135	20	15	42	33	25

TABLE 6.—*Success of Treatment of Patient* with Tabetic Form of Dementia Paralytica with Penicillin After Failure of Malaria Therapy*

Test Number	Date	Wassermann Reactions		Spinal Fluid Findings			
		Blood	Spinal Fluid	Colloidal Gold Curve	Total Protein, Mg./100 Cc.	Pandy Reaction	Cell Count, Cu. Mm.
1.....	2/13/42	4+	4+	55555†	60	4+	225
February 1942—Tertian Malaria (8 paroxysms) and 10 Daily Injections of "Mapharsen" ‡ (0.06 Gm.)							
2.....	9/ 7/42	4+	4+	3344†	35	3+	21
October 1942—Quartan Malaria (9 paroxysms) and 10 Daily Injections of "Mapharsen" ‡ (0.06 Gm.)							
3.....	2/ 4/43	4+	4+	0111†	33	3+	44
January-June 1943—20 Injections of "Melarsen" §							
4.....	6/28/43	4+	4+	2211†	35	3+	5
June 1943-January 1944—20 Injections of "Melarsen"							
5.....	5/29/44	4+	4+	0111†	48	Faint trace	18
6.....	10/ 2/44	4+	4+	1111†	71	4+	160
October 1944—4,000,000 Units Penicillin							
7.....	10/30/44	12	37	84	56	3+	54
8.....	12/ 4/44	12	30	82	45	2+	1
9.....	2/ 5/45	9	21	70	43	Faint trace	8
10.....	5/22/45	6	20	72	44	Faint trace	4
11.....	8/ 6/45	3	12	43	34	Faint trace	3
12.....	1/21/46	4	13	44	31	Faint trace	3
13.....	5/13/46	2	6	48	31	Faint trace	1

* A white man aged 38.

† Readings were made of the first four tubes with the older Lange colloidal gold test.

‡ "Mapharsen" is oxophenarsine hydrochloride.

§ "Melarsen" is a pentavalent arsenical (sesquisodium salt of N-[p-arsonophenyl]-melamine).

|| Titered in units.

¶ The figure represents the sum of readings in all ten tubes with the new Lange method.

cillin or fever will not improve the clinical picture for these patients with transitional abnormal spinal fluid findings.

Among the patients giving satisfactory responses were 3 with dementia paralytica whom we had previously given malaria treatment and large

amounts of chemotherapy, including trivalent and pentavalent arsenical drugs and bismuth preparations, without reducing the cell count of the spinal fluid to normal. Their spinal fluid findings improved satisfactorily after penicillin therapy, and all have now been under observation for more than a year after penicillin was given. Table 6 gives the spinal fluid findings for 1 of these patients before and after treatment with penicillin.

Table 7 contains data on a patient who relapsed after treatment with only 2,000,000 units of penicillin but who responded satisfactorily after retreatment with 8,000,000 units.

The fact that 17 patients were retreated is a reflection less on the effectiveness of penicillin than on the adequacy of the dose. Even with

TABLE 7.—*Response to Retreatment of Patient* with Asymptomatic Neurosyphilis After Failure with 2,000,000 Units of Penicillin*

Test Number	Date	Wassermann Reaction		Spinal Fluid Findings			
		Blood	Spinal Fluid	Colloidal Gold Curve	Total Protein, Mg./100 Cc.	Pandy Reaction	Cell Count, Cu. Mm.
1.....	4/17/44	4+	4+	4444†	25	+	100
2.....	5/16/44	4+	4+	3321†	25	Faint trace	98
May 1944—2,000,000 Units Penicillin							
3.....	5/29/44	100	4+	1221†	21	0	15
4.....	7/31/44	84	4+	1110†	12	0	2
5.....	11/21/44	66	9§	50†	18	0	7
6.....	5/22/45	62	27	107	27	0	70
7.....	6/ 4/45	62	41	122	25	Faint trace	332
June 1945—Retreatment with 8,000,000 Units Penicillin							
8.....	7/ 9/45	53	27	102	24	+	41
9.....	9/11/45	67	19	97	14	0	2
10.....	12/17/45	44	15	58	16	0	1
11.....	3/11/46	41	12	53	13	0	3
12.....	7/ 2/46	27	10	45	16	0	2

* A Negro woman aged 26. The patient had previously been treated with thirty injections of neoarsphenamine and thirty-four injections of "mapharsen" (oxophenarsine hydrochloride).

† Readings were made of first four tubes by the older Lange colloidal gold test.

‡ The figure given represents the sum of readings in all ten tubes with the new Lange method.

§ Titrated in units.

the low dose of penicillin used in many cases, slightly better results were achieved with penicillin than we found after malaria treatment and intensive arsenotherapy.^{2b}

Thus, in our experience penicillin has proved to be a surprisingly effective therapeutic weapon in cases of neurosyphilis. Not only has it proved to be as effective as malaria, in our experience, but it also has the great advantage of being much less dangerous to the patient. Clinical improvement in all groups, including the patients with dementia paralytica, has compared favorably with that following malaria therapy, and we believe that penicillin will ultimately replace fever therapy.

SUMMARY

Criteria for evaluation of therapeutic success in neurosyphilis are discussed.

One hundred and fifty-one patients with active neurosyphilis were treated exclusively with intramuscular injections of penicillin every three hours, the dose and the length of therapy being varied.

One hundred and thirty-five patients (90 per cent) responded satisfactorily; 100 of these were followed for twelve months or more. The longest period of observation was twenty-eight months.

The optimum dose of penicillin is yet to be established, but our experience has led us to adopt a schedule of 40,000 units injected intramuscularly every three hours for one hundred and fifty doses, a total of 6,000,000 units.

Bellevue Hospital.

THE ELECTROENCEPHALOGRAM IN PORENCEPHALY

J. P. MURPHY, M.D.

AND

JOHN S. GARVIN, M.D.

CHICAGO

PORENCEPHALY has been defined as a defect in cerebral or cerebellar structure appearing as a cystlike cavity communicating with the ventricles or separated from them only by a thin layer of brain tissue, covered on the outside by the pia-arachnoid and filled with a clear, colorless fluid.¹ The etiologic factors in this condition, which is usually initiated during the developmental period, may be various—inflammatory process, embolism or thrombosis, internal hydrocephalus or trauma.² Most probably, whatever the fundamental cause, the porencephalic cyst results from ischemic necrosis of the brain tissue and resorption of the products of liquefaction.³

A history of birth injury, failure of growth and paresis of one side of the body, and of convulsive seizures, together with physical findings of spastic hemiparesis, with sensory (particularly topognostic) defect and hypoplasia, is common in cases of porencephaly, since most often this defect of the brain lies in the central region.⁴ Not uncommonly, homonymous hemianopsia is also present and with porencephaly of the occipital lobe may be the only physical finding of significance. Pneumoencephalographic evidence of an air-filled cyst communicating with a ventricle is diagnostic.

De Sanctis, Green and Larkin,⁵ in their study of 3 cases, found the electroencephalogram to be of limited value in confirmation of the

From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine and the Illinois Neuropsychiatric Institute.

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2. Yakovlev, P. I., and Wadsworth, R. C.: Double Symmetrical Porencephalies (Schizencephalies), *Tr. Am. Neurol. A.* **67**:24-29, 1941.

3. Kundrat, H.: *Die Porencephalie: Eine anatomische Studie*, Graz, Leuschner & Lubenski, 1882.

4. Siegmund, H.: Die Entstehung von Porencephalien und Sklerose aus Geburtstraumatischen Hirnschädigungen, *Virchows Arch. f. path. Anat.* **241**:237, 1923

5. De Sanctis, A. G.; Green, M., and Larkin, V. DeP.: Porencephaly, *J. Pediat.* **22**:673-689, 1943.

diagnosis of porencephaly and in localization, electrical tracings giving some indication of the part of the brain involved and occasionally revealing the tendency to convulsions. Pseudoporencephaly (cerebral cyst not communicating with the ventricular system or the result of trauma or abscess formation after the developmental period) has been reported to indicate its presence electroencephalographically in terms of slow waves and spikes.⁶

Nine cases of porencephaly, either true or the result of trauma or abscess, are the subject of this presentation. In all, the diagnosis was established by pneumoencephalography. In all but 1 case the electroencephalogram was abnormal. A definite difference in the amplitude of electrical potentials from homologous areas in the two hemispheres was a consistent finding in the cases of true porencephaly. Slow waves, usually constituting a focus restricted to the lobe of the brain involved, with or without spike seizure discharges, were found in the cases of post-traumatic or postinflammatory cyst when abnormalities were present.

REPORT OF CASES

TRUE PORENCEPHALY

CASE 1.—L. C., a 17 year old white girl, was admitted to the Illinois Neuropsychiatric Institute on July 8, 1942 because of right-sided convulsions of ten years' duration. The family history was without significance save for hereditary left handedness, which the patient also exhibited. An obstetric complication had necessitated the use of forceps at the patient's birth. Difficulty in using the right hand and weakness of the right arm were noted early in infancy. Right-sided jacksonian seizures had occurred at intervals during the previous ten years, and five weeks before admission the patient had a succession of such seizures amounting to status epilepticus.

Physical examination disclosed two palpable grooves (probably forceps marks) along the frontotemporal suture line. The right arm was congenitally atrophic, and the measurements of the right leg were less than those of the left. There was a supranuclear paresis of the right side of the face, and the right extremities were spastic. Reflexes were increased on this side, and the Babinski and Hoffmann signs were elicited. Examinations of the blood, urine and spinal fluid gave results within normal limits. The serologic reactions were negative.

The electroencephalographic record was characterized by generalized 4 to 7 per second activity with prominent asymmetry of amplitude (fig. 1 A), the height of the potential being lower over the entire left hemisphere. There was also generalized, irregular slowing.

The pneumoencephalogram revealed a huge porencephalic cyst in the left occipital region communicating with the ventricle (fig. 2). The wall of the cyst appeared thin, and there was no subarachnoid air overlying it. The ventricular system was shifted to the side of the porencephaly.

6. Goldensohn, L. N.; Marmor, J., and Meyer, B. C.: Pneumo-Encephalographic and Electro-Encephalographic Localization of an Epileptogenic Focus, *J. A. M. A.* **114**:1345-1346 (April 6) 1940.

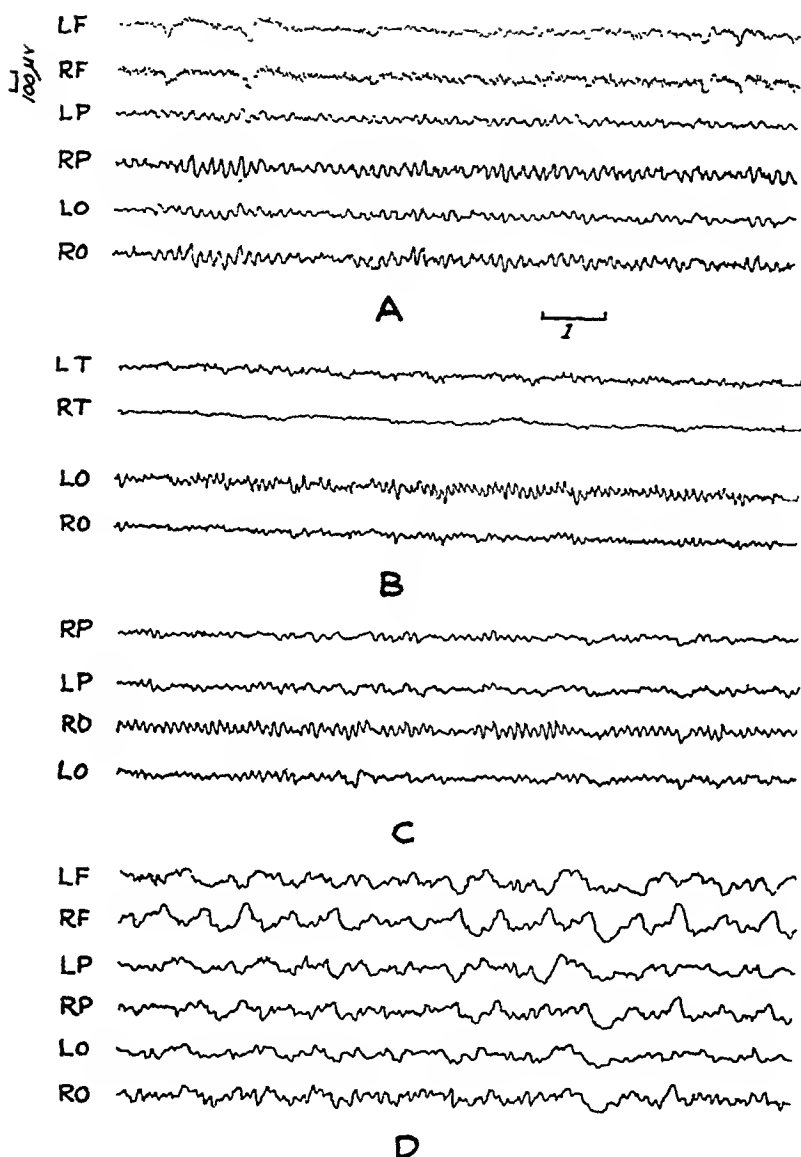


Fig. 1.—Electroencephalograms in cases of true porencephaly. *F* indicates frontal; *P*, parietal; *T*, temporal; *O*, occipital; *R*, right, and *L*, left.

A (case 1), asymmetry of amplitude, especially evident in recordings from the parietal area, with potentials of lower amplitude in the left hemisphere, associated with porencephaly in the left occipital region.

B (case 2), asymmetry of amplitude, most striking in the temporal leads, with potentials of lower amplitude in the right hemisphere, associated with porencephaly in the right occipitotemporal region.

C (case 3), asymmetry of amplitude, notable in recordings from the occipital potentials of lower regions, with lower amplitude on the left side, associated with porencephaly of the left frontocentral region.

D (case 4), asymmetry of amplitude with lower amplitude in the left hemisphere, with many slow waves from the right hemisphere, associated with porencephaly of the left frontoparietal region.



Fig. 2 (case 1).—Posteroanterior pneumoencephalogram, showing a huge porencephalic cyst in the left occipital region with ventricular communication.

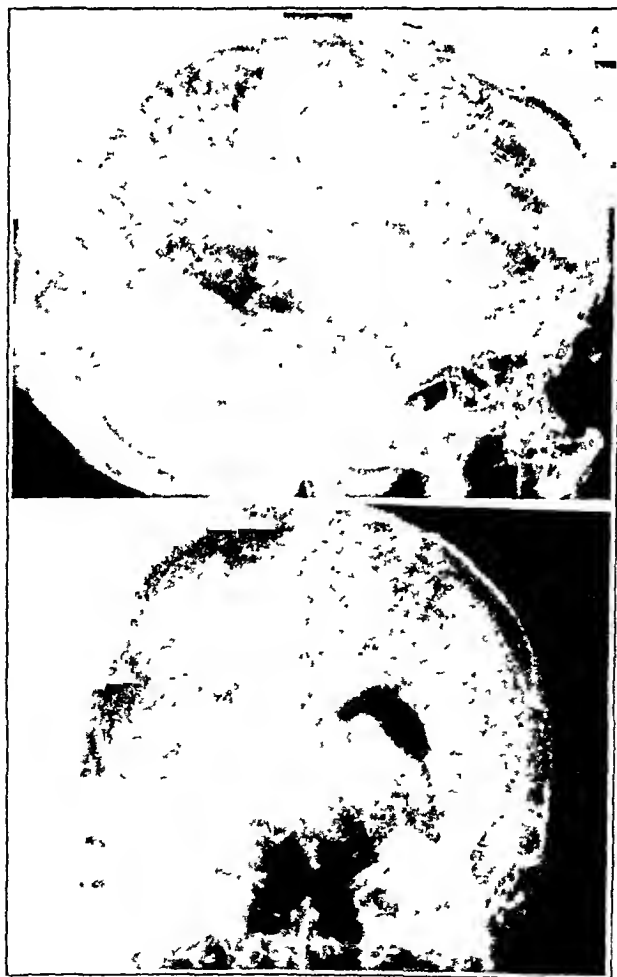


Fig. 3 (case 2).—Above, lateral pneumoencephalogram, showing large porencephalic cyst in the right occipitotemporal area. Below, posteroanterior view, revealing width of the cyst.

CASE 2.—W. S., a white man aged 21, was admitted to the Illinois Neuropsychiatric Institute on Dec. 10, 1945, complaining of moderately severe bifrontal headaches for the preceding five years. The family history was noncontributory. At the age of 8 years the patient was said to have had many convulsive seizures, extending over a period of seven days. There had been no such episodes since that time. He stated that he had been "blind in the left eye" since the age of 8 years.

Physical examination revealed an entirely normal condition except for left homonymous hemianopsia without macular sparing. The usual laboratory examinations, including studies of the spinal fluid and serologic tests, gave normal results.

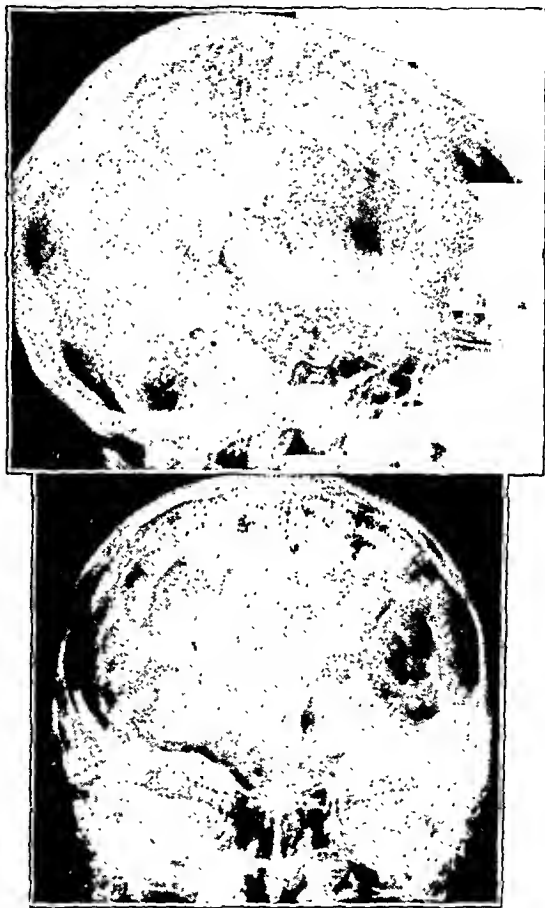


Fig. 4 (case 3).—Above, porencephalic cyst in the left frontocentral region, seen in lateral view. Below, cyst "budding" from the ventricle in anteroposterior projection.

Prominent asymmetry of amplitude was present in the electroencephalogram, with potentials of the lowest amplitude in the right temporo-occipital area (fig. 1 B). Pneumoencephalographic studies disclosed a huge, smooth-walled porencephalic cyst in the right occipitotemporal region in communication with the ventricle (fig. 3). Subarachnoid markings over the cyst and other constituents of the encephalogram were not remarkable.

CASE 3.—W. T., a white youth aged 19, was admitted to the Illinois Neuropsychiatric Institute on April 10, 1946 because of convulsive seizures for the

previous six months. The family history was noncontributory. The patient is said to have sustained a birth injury, resulting in failure of development and weakness of the right side of the body. Fifteen months before admission he had fallen on ice, striking his head, and was rendered unconscious for twenty minutes. There was mild headache for the ensuing twenty-four hours but no other immediate sequelae. For six months prior to admission the patient had experienced infrequent convulsive seizures, with an aura of numbness and tingling in the right arm, jacksonian "march" on the right side with initiation in the hand, and then generalized tonus and clonus.



Fig. 5 (case 4).—Above, lateral view, showing porencephalic cyst in the left frontoparietal region. Below, anteroposterior view, showing extent of cyst and degree of ventricular dilatation.

The boy limped, with a hemiparetic gait. The right extremities, especially the arm and particularly the hand, were smaller than the left. There was typical right spastic hemiparesis without speech disturbances. The superficial modalities of sensation were impaired on the right side below the face, and there were complete atognosia and astereognosia in the right hand. The usual laboratory examinations, including serologic tests and studies of the spinal fluid, gave normal results.

The electroencephalographic record revealed high voltage, 9 per second activity in all leads, with extreme asymmetry of amplitude between homologous areas in the two hemispheres; activity in the left hemisphere was of lower amplitude, and

the asymmetry was most evident in the parieto-occipital areas (fig. 1 *C*). A large, thin-walled porencephalic cyst was seen budding from the wall of the left lateral ventricle in the pneumoencephalogram (fig. 4). The cyst was present in the substance of the left frontal and central regions and was separated from the ventricle proper by a thin septum. There was slight shift of the ventricular system to the side of the cavity.

CASE 4.—F. E., a white man aged 26, was admitted to the Illinois Neuropsychiatric Institute on June 9, 1945 with a history of severe convulsive seizures since the age of 6 years. The past personal and family histories were non-contributory. At 7 years of age the patient had a particularly severe bout of seizures and since that time had been paralyzed on the right side. In 1926 exploration in the left parietal region had been made at another hospital, without any abnormality being encountered.

Physical examination disclosed a mentally dull and torpid person, with a scar in the left parietal region of the scalp. There were nystagmus on left lateral gaze and right spastic hemiparesis, including the face, with hyperreflexia and a Babinski

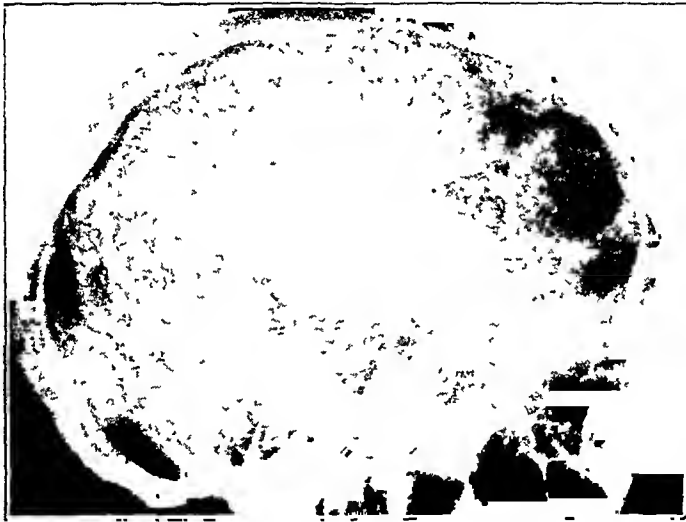


Fig. 6 (case 5).—Cyst of traumatic origin in right frontal area of the brain. The defect in the skull is visible.

sign on that side. The usual laboratory examinations, including serologic tests and studies of the spinal fluid, gave normal results.

The electroencephalographic record consisted of 6 to 9 per second activity in all leads, with extreme asymmetry of amplitude between the hemispheres, the left having the lower amplitude (fig. 1 *D*). During seizures there were many large 3 to 4 per second waves in the right hemisphere and fewer of these abnormal forms in the left hemisphere. Immediately preceding a clinical seizure there were generalized positive spike seizure discharges. The left lateral ventricle was greatly dilated, and there was a large porencephalic cavity in the left frontoparietal region of the brain (fig. 5). The cyst communicated with the ventricle, which was pulled toward it. A bony defect from the operative procedure overlay the dilated ventricle

PSEUDOPORENCEPHALY

CASE 5.—R. Y., a white youth aged 17, was admitted to the Illinois Neuropsychiatric Institute on Feb. 18, 1946 with the chief complaint of convulsive seizures

for the previous four years. At the age of 4 years he had sustained a severe head injury in the right frontal region. This had been treated elsewhere by removal of bone and débridement of the underlying area of the brain. As the patient grew up, he became a problem child and eventually was arrested for stealing cars. For four years prior to admission he had had jacksonian seizures on the left, which spread to involve the entire body. There were a scar and bony defect in the right frontal region but no definite findings of neurologic deficit. The patient was a pathologic liar. Roentgenograms of the skull showed an oval defect in the right frontal bone and calcification in the subjacent portion of the dura or brain.

Electroencephalographic recording demonstrated a focus of 4 to 6 per second activity in the right hemisphere, most prominent in the right frontotemporal area (fig. 7A). Pneumoencephalographic study showed a large cystic defect in the right frontal lobe (fig. 6). There were dilatation and traction of the ventricular system to the right.

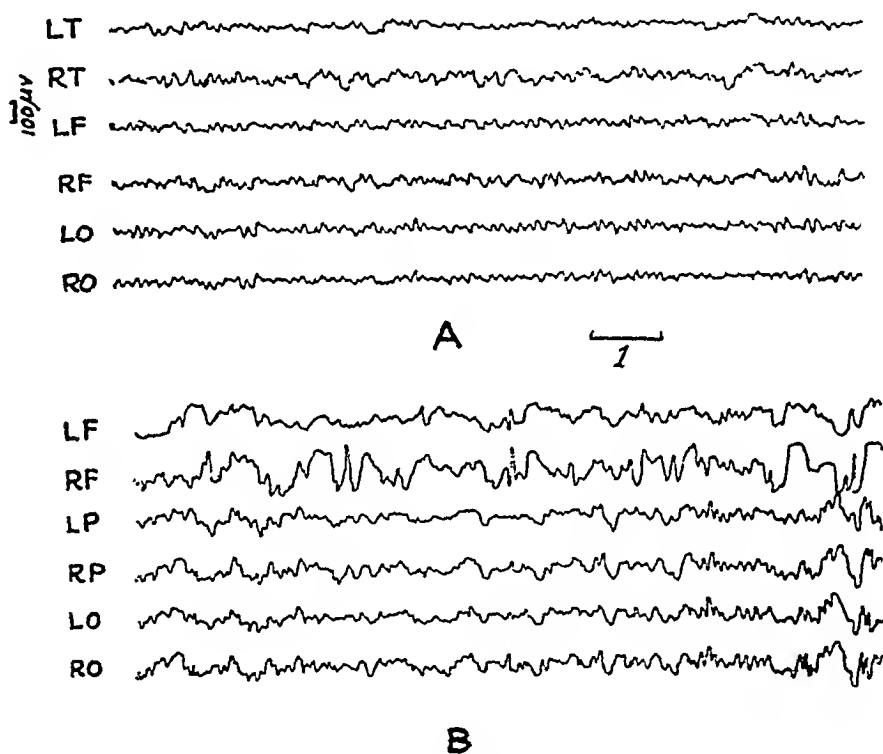


Fig. 7.—Electroencephalographic recordings in cases of post-traumatic cyst of the brain (pseudoporencephaly). *A* (case 5), discharge of slow waves from the entire right hemisphere, most prominent in the frontal lead. The cyst was located in the damaged right frontal lobe. *B* (case 6), focus of large slow wave and another of diphasic spike discharge localized in the right frontal area. The cyst was in the right frontal lobe.

CASE 6.—C. W., a white youth aged 19, was admitted to another institution, electroencephalographic records having been taken at the Illinois Neuropsychiatric Institute. The patient had had generalized convulsive seizures and occasional cramping sensations in the extremities since the age of 9, except for a free interval between the ages of 16 and 18 years. Delivery at birth had been with forceps, and there was a scar in the right frontotemporal region.

The electroencephalogram showed low voltage, irregular activity with a focus of large slow waves and another of diphasic spike activity, sharply localized to the right frontal area (fig. 7B). There were also generalized positive spike seizure

discharges. Pneumoencephalographic study revealed a large cyst in the right frontal lobe, without ventricular communication.

CASE 7.—C. J., a white girl aged 20, was admitted to the Illinois Neuropsychiatric Institute on Jan. 22, 1946 because of convulsive seizures and mental impairment, which had developed since an automobile accident two years previously. There were signs of pyramidal involvement on the right. Two foci of slow wave activity were seen in electrical tracings from the left hemisphere, one in the left frontal and another in the left occipital area. Both lateral ventricles were found to be dilated, the left more than the right; and there was a collection of subarachnoid air, which seemed to communicate with the left lateral ventricle posteriorly.

CASE 8.—H. B., a woman aged 30, was admitted to the Illinois Neuropsychiatric Institute on Feb. 28, 1945 with a history of convulsive seizures during the previous year. Physical examination demonstrated left homonymous hemianopsia with macular sparing, bilateral atrophy of the optic nerves and diminished visual acuity. The protein content of the spinal fluid was 71 mg. per hundred cubic centimeters. The electroencephalogram showed only slight slowing of activity, with a dominant frequency of 7 to 8 per second, and no evidence of focal or lateralized disorder. A ventriculogram revealed a large cystic cavity located paraventricularly in the right parieto-occipital area. Direct communication with the ventricle was questionable, the cyst apparently having been tapped directly (cloudy fluid obtained).

CASE 9.—J. S., a boy aged 7 years, was admitted to the Illinois Neuropsychiatric Institute on April 9, 1945 because of stupor and left hemiparesis. At the age of 8 or 10 months a cerebral abscess developed in the right occipital area as the result of perforation of the skull by a nail. The abscess had been drained, with improvement; but a year later hemiplegia and unconsciousness had developed suddenly. Significant physical findings were a pulsating mass in the right occipital region, left hemiparesis and mental retardation. An electroencephalogram was entirely normal. Pneumoencephalographic examination disclosed a cyst in the right occipital region, which probably communicated with the ventricle.

COMMENT

Jasper and associates⁷ were first to correlate asymmetry of amplitude in the electroencephalogram with lesions of the brain, noting the presence of this abnormality in cases of subdural hematoma. Gibbs⁸ stated that such asymmetry may be seen in a variety of conditions, including hematoma, cerebral aneurysm, concussion and lesions of the visual system.

We would add true porencephaly to the list of conditions productive of lateral asymmetry of amplitude in the electroencephalogram and further suggest an association of this type of electrical change with the undoubted vascular occlusive factor in the pathologic entity. Asymmetry

7. Jasper, H. H.; Kershman, J., and Elvidge, A.: *Electroencephalographic Studies of Injury to the Head*, Arch. Neurol. & Psychiat. **44**:328-348 (Aug.) 1940.

8. Gibbs, F. A.: *Electrical Activity of the Brain*, in Luck, J. M.: *Annual Review of Physiology*, Stanford University, Calif., Annual Reviews, Inc., 1945, vol. 7, pp. 427-454.

of amplitude has been noted in cases of homonymous hemianopsia⁹ and in such circumstances has been thought to be due to interruption of the geniculocalcarine pathways. The visual projection system was certainly cut across by a porencephalic cyst in cases 1 and 2. In cases 3 and 4, however, the cyst lay frontally, and physical examination revealed no evidence of defect in the visual fields. In the experience of Strauss, Liberson and Meltzer,^{9a} abnormally high degrees of asymmetry are found most frequently in cases of cerebrovascular lesions with involvement of one hemisphere. Sugar¹⁰ observed a high incidence of asymmetry of amplitude in cases of migraine, the lower amplitude occurring on the side of the brain involved, as indicated by neurologic examination, and not necessarily on the same side as the headache. Apparently, then, interference with a major vascular supply to one side of the brain can produce lowering of amplitude of potentials from this side. It is possible that this electroencephalographic abnormality may be indicative of permanently deficient circulation in cases of true porencephaly.

In 3 of the 5 cases of pseudoporencephaly (cases 5, 6 and 7) foci of slow waves were manifested in the region corresponding to cerebral damage, with slowing of potentials from the rest of the hemisphere involved. In case 6, featured clinically by convulsive seizures, diphasic spikes were seen from the cortex overlying the cyst.

The only abnormality found in the electroencephalogram in case 8 was slight, general slowing. Records from case 9 (postinflammatory cyst) were entirely normal.

SUMMARY

The electroencephalographic findings in 9 cases of porencephaly, 4 of true porencephaly and 5 of pseudoporencephaly (post-traumatic or postinflammatory), are presented, with pneumoencephalographic confirmation of the diagnosis.

Asymmetry of amplitude of potential, the lower amplitude being on the side of the lesion, was a consistent finding in the cases of true porencephaly. In 2 of the 4 cases of this category the geniculocalcarine pathways were interrupted, but in 2 the cyst was present frontally and there was no evidence of involvement of the optic radiation. It is suggested that asymmetry of amplitude in cases of true porencephaly may be indicative of deficient cerebral circulation on the side of the lesion.

9. (a) Strauss, H.; Liberson, W. T., and Meltzer, T.: *Electroencephalographic Studies: Bilateral Differences in Alpha Activity With and Without Cerebral Pathology*, J. Mt. Sinai Hosp. **9**:957-962, 1943. (b) Case, T. J.: *Alpha Waves in Relation to Structures Involved in Vision*, Biol. Symposia **7**:107-116, 1942.

10. Sugar, O.: *Asymmetry in Occipital Electroencephalograms*, Dis. Nerv. System **8**:141 (May) 1947.

Foci of slow waves localized to the part of the brain involved were found in the records of 3 cases of pseudoporencephaly (post-traumatic). Slowing of potential was manifest in tracings from the rest of the ipsilateral hemisphere. In 1 case of cerebral cyst (probably postinflammatory) the electroencephalogram showed only slightly slow activity, and in another (in which the cyst followed an abscess) the electrical records were entirely normal.

Electroencephalographic records were taken under the direction of Dr. and Mrs. Frederic A. Gibbs. Photographs were made by Mr. Willard Huntzinger.

University of Illinois College of Medicine.

THE ELECTROENCEPHALOGRAM IN POLIOMYELITIS

BERNARD L. PACELLA, M.D.

CLAUS W. JUNGEBLUT, M.D.

NICHOLAS KOPELOFF, Ph.D.

AND

LENORE M. KOPELOFF, Ph.D.

NEW YORK

BECAUSE of the dearth of knowledge concerning metabolic changes caused by poliomyelitic infection of the central nervous system, it appeared of interest to study possible electrophysiologic alterations of the brain during the course of the disease. Electroencephalograms were therefore taken of rhesus monkeys and of guinea pigs with experimental infection with simian or murine virus. In addition, 17 persons with postpoliomyelitic paralyses were studied.¹

Five monkeys were given intracerebral injections of simian virus into the right frontal area: Three received the RMV strain (0.5 cc. of viral cord suspension [1:10 or 1:100]); and 2, the Aycock strain (0.5 cc. of a 1:50 suspension). Two additional monkeys served as controls: One was given an intracerebral injection of 0.5 cc. of a 10 per cent Aycock cord suspension inactivated by boiling for twenty minutes, and the other received 0.5 cc. of isotonic solution of sodium chloride. Ten guinea pigs were infected with murine poliomyelitis virus (mouse-adapted strain of human MM poliomyelitis virus)²: Five received 0.1 cc. of a 1:10 viral mouse brain suspension intracerebrally, and 5 received 1 cc. of a 1:10 suspension intra-abdominally.

Electroencephalograms were taken from the experimental animals immediately prior to inoculation and at intervals during the course of the disease. A head

This study was aided by a grant from the Philip Hanson Hiss Jr. Memorial Fund.

From the Departments of Experimental Psychiatry and Bacteriology, New York State Psychiatric Institute, and the Department of Bacteriology, Columbia University College of Physicians and Surgeons.

1. These patients were made available through the courtesy of Dr. Kenneth Landauer, Superintendent, New York State Reconstruction Home, West Haverstraw, N. Y.

2. Jungeblut, C. W., and Dalldorf, G.: Epidemiological and Experimental Observations on the Possible Significance of Rodents in a Suburban Epidemic of Poliomyelitis, *Am. J. Pub. Health* **33**:169, 1943. Jungeblut, C. W.: Serological Relationships Within the Poliomyelitis Group of Viruses, *ibid.* **34**:259, 1944; Studies in Rodent Poliomyelitis: VI. Further Observations on Interference Between Murine and Simian Strains of Poliomyelitis Virus, *J. Exper. Med.* **81**:275, 1945.

control apparatus attached to an animal board was used to immobilize the blindfolded monkeys. Curare ("intocostrin") was administered intravenously when necessary in a dose approximating 1 mg. per kilogram of body weight. Such small doses of curare were without significant effect on the electroencephalogram or the infection. This procedure had been previously carried out on monkeys in at least twenty control examinations. Blindfolded guinea pigs tied to an animal board remained sufficiently quiet to make the administration of curare unnecessary. Electroencephalograms were taken with a two-channel standard apparatus, utilizing a bipolar system of recording. A portable two-channel electroencephalograph was used to obtain tracings from the paralytic patients. The electrodes consisted of small needles firmly affixed to the scalp, over the corresponding prefrontal, motor and occipital regions of both sides of the head.

RESULTS

Monkeys.—In all 3 monkeys infected with RMV virus there was an elevation of temperature within seventy-two hours, with symptoms of paralysis appearing on the fifth or sixth day after inoculation. Death occurred between the ninth and twelfth days.

The 2 monkeys given injections of the Aycock strain exhibited an elevation of temperature on the fifth day after inoculation, with symptoms of complete paralysis on the eighth and the thirteenth day, respectively. The first monkey was killed, while the second animal died on the fourteenth day.

Electroencephalographic abnormalities were classified as slight, moderate or severe, depending on the frequency and incidence of slow activity, irregularity of pattern and amount of high voltage fast activity. Electroencephalographic tracings for normal monkeys had been previously described³ and were used for comparison with the records of the infected animals. For the patients, electroencephalographic abnormalities were evaluated according to the standard criteria in current use, including the presence of delta activity, irregular features and high voltage fast activity.

None of the animals exhibited any definite electroencephalographic abnormality prior to the onset of fever or of clinical symptoms. However, coincident with the elevation of temperature on the third or fourth day, the 4 monkeys infected with the RMV strain showed a slight to moderate increase in the incidence and amplitude of alpha rhythm, and in fast activity. After the fifth or sixth day, whether the temperature remained elevated or not, there were a decreased incidence of alpha waves, a lowered voltage output, a relative increase in fast frequencies and an increase in the 6 to 8 cycle per second activity. The animals at this time exhibited generalized weakness and beginning paralysis. As the paralytic symptoms became more pronounced, there

3. Pacella, B. L.; Kopeloff, N.; Barrera, S. E., and Kopeloff, L. M.: Experimental Production of Focal Epilepsy, *Arch. Neurol. & Psychiat.* **52**:189 (Sept.) 1944.

were noted a greater incidence of slow activity, consisting chiefly of 5 to 7 cycle per second waves; random 4 cycle per second potentials; disappearance of alpha rhythm with a relative increase in the amount of fast activity, and a lowered voltage output. The 2 monkeys inoculated with the Aycock strain showed no definite changes in the electroencephalogram during the incubation period until paralysis set in. At this time the tracings revealed features similar to those noted in the animals inoculated with the RMV strain during the corresponding stage.

Electroencephalograms were taken daily on the 2 control animals for five days following intracerebral injection of inactive material, during which time they showed no symptoms. No abnormality or change in the electroencephalographic pattern was noted in the monkey given injections of isotonic solution of sodium chloride. The other animal showed lowered voltage output, decreased incidence of alpha rhythm and an increase in the amount of fast activity, which appeared twenty-four hours after the injection of heated cord suspension. A similar pattern was observed on the succeeding days of observation, but the changes never reached the intensity observed in monkeys inoculated with live virus.

The early appearance of increased amplitude and fast activity, associated with elevation of temperature in the preparalytic stage, may have been related to cerebral lesions resulting from progress of the virus from the intracerebral portal of entry to the spinal cord. Certainly the trauma of inoculation was not responsible for the electroencephalographic changes observed, since there was no evidence of a focal disturbance. These early changes, therefore, may carry some significance; however, somewhat similar tracings may be occasionally observed in the case of "normal" monkeys. The appearance of slow waves and the disappearance of alpha rhythm noted during the paralytic stage presented a definitely more abnormal picture.

Guinea Pigs.—Of the 5 guinea pigs given intracerebral injections, there was clinical evidence of infection in every case. Two animals died with flaccid paralysis of the hindlegs; 2 died without paralysis (which may have occurred but was not observed), and 1 had flaccid paralysis and recovered. Of the 5 guinea pigs given intra-abdominal injections, 1 died with paralysis; 1 died without paralysis, and 3 showed no clinical signs. In only 1 animal was a slight elevation of temperature noted.

Electroencephalographic tracings taken daily, beginning forty-eight hours before and continued for eighteen consecutive days after inoculation, failed to reveal any consistent or significant changes in pattern.

Paralytic Patients.—Electroencephalograms were taken on 17 patients convalescing from poliomyelitis, all of whom had exhibited severe

residual paralysis two and a half to fifteen months after the onset of acute symptoms. The tracings of 2 patients (respirator patients with bulbar paralysis) showed definite abnormality; those of 5, borderline abnormality (all were under 18 years of age), and those of 10, a normal pattern. However, the incidence of electroencephalographic abnormality in apparently normal persons might be of a similar order. This series is, therefore, too small to be significant for statistical evaluation. But the relatively large number of borderline tracings would seem to warrant further study of possible residual cerebral changes resulting from the infection. There was no correlation between laterality of peripheral paralysis and electroencephalographic findings in the cases of abnormal and borderline tracings. In all instances the electroencephalographic disturbance, when present, was of a diffuse nature.

COMMENT

The absence of any significant electroencephalographic abnormality during the period of incubation or the preparalytic stage in monkeys experimentally infected with simian poliomyelitis virus suggests that the electroencephalogram would be of doubtful diagnostic value in detecting poliomyelitic infection in man prior to the onset of paralysis. The electroencephalographic abnormalities observed in monkeys during the paralytic stage may have been due to encephalitic changes brought about by the artificial mode of inoculation. However, other factors, such as continued elevation of temperature and inanition with associated metabolic changes, may have contributed to the electroencephalographic disturbances even before notable encephalitic changes had occurred.

It was of interest to note that with guinea pigs given either intracerebral or intra-abdominal injections of the murine strain of poliomyelitis, electroencephalograms taken during the preparalytic, as well as the paralytic, stage showed no significant abnormalities. Clinically the guinea pigs showed no encephalitic symptoms but presented a picture of flaccid paralysis confined to the extremities.

Of the small series of convalescent patients examined, only 2 exhibited definitely abnormal electroencephalographic patterns. It is significant that both these patients had been maintained in the respirator for some time, and their illness could probably be diagnosed as polioencephalitis. Since classic poliomyelitis is essentially an infection with localization in the anterior horn of the spinal cord, the absence of electroencephalographic changes in most of our tracings, which were limited to the recording of cerebral activity, is not surprising. Whatever definite electroencephalographic disturbances were observed

appeared to be associated with the polioencephalitis caused by the experimental infection in monkeys or with the infrequent cases of bulbar involvement in man.

SUMMARY

1. No definite or consistent electroencephalographic changes which might indicate abnormal electrocortical activity were observed prior to the onset of fever or paralysis in monkeys given intracerebral injections of either the RMV or the Aycock strain of simian poliomyelitis virus. Abnormalities in the electroencephalogram appeared during the paralytic stage and became more conspicuous with the progression of symptoms. The electroencephalographic changes consisted chiefly in a progressive increase of slow activity, disappearance of alpha rhythm, a relative increase in the amount of fast activity and a lowered voltage output.

2. No electroencephalographic abnormalities were noted in guinea pigs given either intracerebral or peripheral injections of murine poliomyelitis virus in the presence or absence of paralytic symptoms.

3. Of 17 patients convalescent from poliomyelitis, all of whom had severe residual paralysis, 2 exhibited definite electroencephalographic abnormality and 5 showed a borderline disturbance. The remaining 10 patients had normal electroencephalograms.

New York State Psychiatric Institute, 722 West One Hundred and Sixty-Eighth Street (37).

Columbia Medical Center, 630 West One Hundred and Sixty-Eighth Street (32).

EFFECT OF CROSSING NERVES TO ANTAGONISTIC LIMB MUSCLES IN THE MONKEY

R. W. SPERRY, Ph.D.

CHICAGO

CROSSING of nerves to antagonistic limb muscles or transplantation of the muscles themselves has been found to produce in the rat disorders of motor coordination directly correlated with the anatomic rearrangements. For example, transposition of the flexor and extensor muscles of the shank¹ or interchange of the nerve supply of these muscles² produced in each case a full reversal of the flexor-extensor movements of the ankle. A comparable reversal of motor action in the forelimb was shown to follow the crossing of nerves and the transposition of muscles acting on the elbow joint.³ Sensory nerve crosses from one hindfoot into the contralateral hindfoot also were found to result in false reference of sensations and a maladaptive reversal of the withdrawal reflexes.⁴ All these functional derangements persisted permanently in the rat without correction by reeducation.

Numerous clinical reports indicate, however, that man is capable of achieving motor readjustments considerably more complex than those called for by the foregoing nerve-muscle operations on the rat.⁵ Consequently, it seemed imperative to conduct experiments of the sort

This work was done at the Yerkes Laboratories of Primate Biology as part of a project directed by Dr. Paul Weiss under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

1. Sperry, R. W.: The Functional Results of Muscle Transposition in the Hind Limb of the Rat, *Anat. Rec. (supp.)* **73**:51, 1939; *J. Comp. Neurol.* **73**:379-404, 1940.

2. Sperry, R. W.: The Effect of Crossing Nerves to Antagonistic Muscles in the Hind Limb of the Rat, *J. Comp. Neurol.* **75**:1-19, 1941.

3. Sperry, R. W.: Transplantation of Motor Nerves and Muscles in the Forelimb of the Rat, *J. Comp. Neurol.* **76**:283-321, 1942.

4. Sperry, R. W.: Functional Results of Crossing Sensory Nerves in the Rat, *J. Comp. Neurol.* **78**:59-90, 1943; Fixed Persistence in the Rat of Spinal Reflex Patterns Rendered Extremely Maladaptive by Cross Union of Sensory Nerves, *Federation Proc.* **5**:98, 1946.

5. Sperry, R. W.: The Problem of Central Nervous Reorganization After Nerve Regeneration and Muscle Transposition: A Critical Review, *Quart. Rev. Biol.* **20**:311-369, 1945.

described for the rat on an intermediate form, such as the monkey. It was not intended in the present investigation to try to explore in full quantitative detail the capacities of the monkey for readjustment under such conditions. This would be a tremendous task, requiring, among other things, a preliminary analysis of normal muscle kinesiology beyond anything yet available, even for man. The object was, rather, to disclose, if possible, any basic and major differences in capacity for readaptation between the rat and the monkey that might appear under experimental conditions which were roughly similar, and to find out whether the results in the monkey would not approach closely those reported for man. It was hoped that such a comparison of the monkey and the rat might yield some clues to fundamental differences in organization of the central nervous system of these two forms which might explain in part the superior adaptability of the primates.

METHOD AND MATERIALS

The nerve branches to the primary flexor and extensor muscles of the elbow were dissected free, divided and cross united, so that the nerves were forced to regenerate into muscles antagonistic to those which they had formerly supplied. Nerves of the arm, rather than of the leg, were chosen because, other things being equal, motor readjustment should occur more readily in the arm.⁵ Selection of these particular nerves and muscles acting on the elbow joint was made because of anatomic advantages for the type of operation involved, because the muscle function at this hinge joint is relatively uncomplicated and because the same nerves and muscles had been used in previous experiments on the rat.

After sufficient time had been allowed for nerve regeneration, the movements of the elbow were examined in natural and in trained activities, first for reversed movements and discoordination and later for evidence of correction of these abnormal movements. Because the animals soon learned to use the elbow joint by various trick methods without any active contraction of the test muscles, it became necessary to test coordination and to train for reeducation under special conditions in which such trick movements would not be possible. This was satisfactorily accomplished by making the monkeys reach through a metal tube for their food (figure). The tube was about the length of the monkey's upper arm and was large enough so that the fist partly closed over a small object could easily be drawn through it. The tube was mounted over a hole in the center of a large screen of hardware cloth, the mesh of which was too small to permit passage of the fingers but permitted the animal to see easily the object for which it was reaching. The screen and tube could be placed on the sides or on the top of the training cages. Pieces of food impaled on a stick were held outside the screen in such a position that they could be reached only if the monkey extended the arm into the tube all the way to the shoulder, with the elbow protruding slightly beyond the outer edge of the tube. In this position the elbow could be flexed and extended freely, but the upper arm and the shoulder were well stabilized in and against the tube. Elbow movement was easily observed under these conditions, and most of the trick movements depending on shoulder action, momentum or inertia of the forearm or special postures with respect to gravity were excluded. By holding the lure in different positions with respect to the end of the tube, by moving the lure after the animal had started to reach for it, and by using the tube

in vertical as well as in horizontal positions, one could test satisfactorily the monkey's capacity to flex and extend the elbow under a variety of conditions.

Use of the tube was begun shortly after recovery of function in the second arm in the bilateral cases. Approximately twenty trials per day for each arm were given through the first seven weeks. Thereafter the tests were administered over ten day periods at intervals beginning about once in every two months and increasing to once in six months at the end of the third year.

Observations were carried out over a total period of a little more than three years. Most of the data were obtained from 4 red spider monkeys (*Ateles geoffroyi*), 3 of them with nerves crossed in both arms and 1 with nerves crossed in one arm only. These full-grown animals had been kept in captivity at least six years prior to their use in these experiments. Additional results obtained on

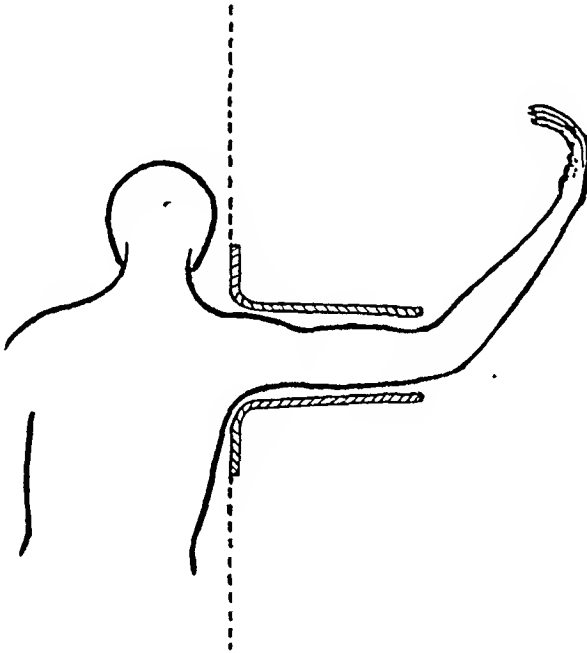


Diagram showing how elbow movements were tested by having the monkey reach through a short rigid tube.

2 macaques (*Macaca mulatta*) both operated on unilaterally, were in essential aspects similar to those obtained on the spider monkeys. The macaques were approximately 3 years old at the time of operation. They proved to be somewhat less satisfactory than the spider monkeys with regard both to the operation and recovery and to functional examination. One of the spider monkeys died at the end of one year and another at the end of the second year. The other 4 animals were killed about three and one-half years after their initial nerve-crossing operation. An additional spider monkey and a macaque, in both of which the elbow joint became ankylosed after operation, were discarded from the experiment.

The following control measures were taken: In all animals all extra muscles acting directly on the elbow joint were excised in order that their action might not counteract or obscure that of the test muscles. In the contralateral arm of

the spider monkey with unilateral nerve cross, nerve splices were made but failed to hold, and the nerves regenerated back into their proper muscle groups instead of into antagonistic muscles. Otherwise, this arm was operated on in the same way as in the other spider monkeys. It therefore made a good control and was used as such. To overcome the animals' tendency not to use an arm that had been operated on, the other arm was either similarly operated on, or, in the unilateral cases, paralyzed by repeated nerve crushing. Special care was taken throughout all tests to distinguish movement of the elbow caused by active contraction of the test muscles from movement produced by other methods. Biopsy was performed about two years after the first operation to check, by dissection and by electrical stimulation of the nerves proximal to the point of cross union, for the intended cross innervation as well as for any possible misregeneration of nerve fibers back into their original muscles. Again, when the animals were killed, the arms were dissected carefully, and electrical stimulation was employed to test once more for the existence of stray nerve fibers innervating their own, instead of antagonistic, muscles.

OPERATION PROCEDURE

The main trunk of the musculocutaneous nerve, which supplies the biceps and brachialis (flexor) muscles of the elbow, was dissected free and cut. Likewise, the nerve branches to the triceps (extensor) muscles were dissected free and cut at the same level. In freeing the extensor nerves, it was frequently necessary to split the nerve branches for several centimeters into their constituent loosely bound fascicles. This was done under a dissecting microscope with almost no difficulty in this region from intraneural plexuses. The central end of the musculocutaneous nerve was then united to the collected distal ends of the triceps nerves; conversely, the central ends of the triceps nerves were united to the distal end of the musculocutaneous nerve. Because there was no slack in the nerve lengths, the crossed stumps were fastened together, with only a small gap between them, by a single suture of fine silk through the epineurium. A tube of preserved monkey artery about 1.7 cm. in length was then pulled over each union. Finally, further to prevent any fibers from misregenerating into their original channels, a large sheet of allantoic membrane⁶ ("insultic membrane") was laid between the two splices.

The coracobrachialis muscle was excised, and its nerve was split proximally away from the musculocutaneous trunk, so that no nerve fibers to this muscle were included in the nerve cross. The end of this nerve was ligated and fastened proximally to prevent regeneration into the test muscles. The anastomotic nerve branch from the median nerve to the brachialis muscle was also severed, ligated and tied posteriorly, where it could not regenerate into its original muscle. The epitrochlearis (extensor) muscle and its nerve were left intact to help prevent ankyosis of the joint during the period of muscular paralysis. About six months after the primary operation this muscle was excised and its nerve ligated and fastened as far dorsally as possible. At the same time the muscles of the forearm which overlap the elbow joint and have their origin on the humerus, such as the brachioradialis, the pronator teres and the extensor carpi radialis longus, were excised to prevent their aiding in movement of the elbow. It has been shown that

6. "Insultic Membrane" (Bauer and Black).

flexion of the elbow can be accomplished in man by some of these muscles after complete paralysis of the brachial flexors,⁷ and such action is even more favored by the mechanical relations of these muscles in the monkey.

The method just described was used in crossing the nerves in the right arm of the 4 spider monkeys. An alternative procedure was used on the left arm of these animals and also on the left arm of the 2 macques as follows: The overlapping muscles of the forearm were excised in a preliminary operation about one month before the nerves were crossed. In the main operation, the central ends of some of the more proximal branches of the nerves to the triceps muscle were collected and crossed to the distal stump of the isolated nerve to the biceps muscle. The central end of the nerve to the brachialis muscle was crossed to the collected distal stumps of some of the more peripheral branches to the triceps muscle. When crossed in this way, the nerve stump could be joined with plenty of slack, and no silk suture was required. The nerves were trimmed to an appropriate length and joined in an arterial tube by a method similar to that advocated by Weiss.⁸ The unused nerve stumps were ligated tightly and tied to tissues as far away from their original terminations as possible. The epitrochlearis muscle and nerve were left intact, to be excised about six months later. All operations were carried out with the subject under deep pentobarbital anesthesia.

No essential differences in the functional results were noted which could reliably be attributed to the different surgical methods of crossing. The essential effect of the operations by either method was to cause the flexor muscles of the elbow to become innervated only by what were originally extensor motoneurons, and the extensor muscles to be innervated only by flexor motoneurons such that a reversal of elbow movement should result in the absence of central nervous reorganization. Such terms as "reversed movement" and "reversed action" refer throughout to the unadjusted maladaptive action of the reinnervated muscles.

RECOVERY WITH REVERSED MOVEMENTS

Immediately after the operation on the right arm, the animals used the contralateral arm almost entirely. After the wound had healed, and while the nerves were still regenerating, the use of the experimental arm gradually increased, although the left arm remained dominant and preferred. The onset of recovery in the test muscles of the right arm was thus obscured by the tendency to use the normal (left) arm, as well as by the action of extrabrachial and antibrachial muscles left intact during the period of muscular paralysis to help prevent ankylosis of the joint. Removal of these extra brachial muscles again decreased the use of the right arm. Even when the overlapping muscles of the forearm had been freshly excised from the left arm, in the preliminary operation for the alternative surgical procedure previously described, the animal still preferred immediately afterward to use the left arm.

It was only later, after the nerves had been crossed or crushed in the contralateral arm, approximately eight months after the primary

7. Wright, W. G.: *Muscle Function*, New York, Paul B. Hoeber, Inc., 1928.

8. Weiss, P.: *The Technology of Nerve Regeneration: A Review; Sutureless Tubulation and Related Methods of Nerve Repair*, *J. Neurosurg.* **1**:400-450, 1944.

operation in all cases, that signs of function of the crossed nerves became apparent. When the animals were thus suddenly forced to use the arm with the cross innervated muscles in ways to which they had not been accustomed, they displayed reversed flexion and extension movements of the elbow. For example, in an attempt to extend the arm outward and forward horizontally for food, the forearm was, instead, flexed upward against gravity toward the chin. When the monkey tried to catch food impaled on the end of a stick, which was moved about slowly in front of the cage within easy reach, the elbow showed extension when flexion was called for, and vice versa. When the arm was being withdrawn through the wires of the cage, the forearm often flexed at right angles instead of straightening, thus becoming caught at the elbow. Efforts to straighten the arm only caused it to bend more acutely. Caught in this position, the animal would continue to tug and pull for some moments, until eventually the flexor muscles relaxed, the elbow straightened and the arm was pulled inside the cage.

Reversed movements of the sort just described appeared in all the 4 spider monkeys and in 2 macques, varying in intensity and frequency, however, in the different animals. They were most conspicuous in a spider monkey in which the muscles of the forearm and hand, as well as the test muscles of the upper arm, were paralyzed during the period of regeneration. This paralysis was probably caused by overstretching of the main nerve trunks, particularly of the radial nerve, at the time of operation. Consequently, this animal used the right arm hardly at all during the period of regeneration and, unlike the other animals, had had no practice in inhibiting the reversed action of the test muscles or in using the elbow passively during the preceding months.

In animals with bilateral crossed innervation the time of onset of functional recovery in the left arm was obscured in the spider monkeys mainly by trick methods of using the elbow joint passively and, in part, by preferential use of the right arm, which had previously been operated on. The animals were not suddenly forced to use the left arm in new ways, as had been the case with the right arm. There was plenty of time during recovery to adjust gradually to the postoperative conditions; consequently, reversed action was not seen in the left arm of these monkeys under natural cage conditions. It was only when they were forced to use the left arm in reaching through the metal tube, where the trick movements on which they had been relying were impossible, that reversal of elbow action on the left side became definitely apparent.

In 1 spider monkey recovery on the left side was exceptional in that no reversal of movement appeared under any conditions. On the contrary, well coordinated flexion and extension of the elbow in the proper direction occurred even in comparatively rapid movements. Biopsy, as well as examination after the animal had been killed, revealed that in this

instance the nerve crosses had not been successful. The nerve splices had pulled apart, and extensive misregeneration of nerve fibers into their original flexor and extensor muscle groups had taken place. Almost no crossed innervation was observed. The action of the reinnervated muscles of this limb therefore presented a good control for comparison with the function in those animals in which the nerve crosses had been successful.

On the whole, the reversed movements in the monkeys were much less conspicuous than had been the reversed limb movements in the rat after similar nerve crossing operations. In the rat the reversed responses were carried out with full intensity and scope persistently throughout all activities, the animals seemingly insensible of the reversal. In the monkey, on the other hand, the occurrence of a movement in reverse direction usually caused a break in the general activity going on at the moment. The erroneous reaction was halted and attention was turned to the abnormally acting member. After repeated attempts to improve the arm movement, the animal either succeeded somehow in getting the hand into a satisfactory position, or ceased trying altogether. As a result, and because of other factors to be mentioned, the reversed elbow movements tended to be weak in the monkey and in most instances to be brief or only incipient, without being carried through to completion.

The idea that central nervous reorganization to suit the new peripheral relations under such conditions occurs immediately and spontaneously, without any practice,⁹ a view which has clearly been discredited in the case of the rat and lower vertebrates,¹⁰ is also refuted by these results in the monkey. Not only did reversed movements appear during the early stages following nerve regeneration but, as will be described, the reversed action persisted in some instances for months, and even years.

After the early stages of recovery the test and observation program proceeded in an exploratory manner, with considerable irregularity and variation from animal to animal and from time to time. It would be prohibitive to recount in any detail the histories and specific findings for the individual animals throughout the three year period. An attempt is made, therefore to present the essential aspect of the results under the following topical headings, with examples illustrating the principal points in each instance.

9. Marina, A.: Die Relationen des Paläencephalons (Edinger) sind nicht fix, *Neurol. Centralbl.* **34**:338-345, 1915. Bethe, A., and Fischer, E.: Die Anpassungsfähigkeit (Plastizität) des Nervensystems, in Bethe, A.; von Bergmann, G.; Einbden, G., and Ellinger, A.: *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1931, vol. 15, pp. 1045-1130. Goldstein, K.: *The Organism*, New York, American Book Co., 1939.

10. Sperry.⁵ Weiss, P.: Self-Differentiation of the Basic Patterns of Co-Ordination, *Comp. Psychol. Monogr.* **17**:1-96, 1941.

TRICK MOVEMENTS AND SUBSTITUTIONARY REACTIONS

The monkeys were quick to find ways of using the experimental limb advantageously without contracting the test muscles. These compensatory, or "trick," methods of using the elbow passively were largely acquired early in the regeneration period, while the test muscles were completely paralyzed, and were then carried over with gradual improvement after the crossed nerves had regenerated. The ability to use the arm in such a way that the elbow would flex and extend passively as early as three weeks after the final removal of the extrabrachial muscles in the cases of bilateral crossed innervation was so good that a casual observer might well have failed to notice any motor disability. The efficiency with which the arms were used in regular cage activities suggested at first glance that complete central nervous reorganization must already have occurred, enabling the test muscles to contract in their proper action phase despite the abnormal innervation. With more careful analysis of the movements, however, it became apparent that this elbow action was not necessarily dependent on active contraction of the test muscles. In every situation observed, all flexor movements and all but a few rare extensor movements (see section on "Positive Readaptation") could be accounted for on the basis of other factors, such as gravity, inertia or secondary effects of muscles at other joints.

Extension of the elbow was easily achieved and maintained in most postures by the action of gravity. The forearm was simply allowed to fall loosely from the elbow into the extended position. In some postures the relative positions of elbow and forearm were adjusted by movement of the upper arm from the shoulder, so as to increase the effectiveness of gravity. At times the movement from the shoulder, combined with the inertia of the forearm, was sufficient to bring about extension of the elbow without the aid of gravity. When it was necessary to extend the arm upward against gravity, as in climbing, the elbow was usually extended first by gravity, and then the whole arm, straightly extended, was raised from the shoulder. At the same time the upper arm was properly rotated so that the weight and inertia of the forearm and hand tended always passively to extend the elbow, which, of course, would not bend beyond the straight position because of the structure of the bones and ligaments. With the upper arm in a horizontal position or at a downward angle, the flexed elbow could be extended simply by outward rotation of the arm from the shoulder, in which case the rotation of the upper arm swung the forearm into a position from which it was forced into extension by gravity.

Flexion of the elbow, which has to occur against gravity in most upright postures, was not achieved as frequently as extension. To flex the elbow upward to bring food to the mouth, the animal usually

propped the forearm against the knees in the sitting position. The elbow was sometimes flexed by gravity when the upper arm was raised. The spider monkeys frequently picked up food and put it in the mouth while hanging upside down from their tails. In this position the forearm hung vertically from the elbow and was flexed or extended passively as the elbow was raised or lowered. Occasionally the forearm was swung into a position of flexion by a flail-like motion. When the hand grasped the wires of the cage, flexion or extension of the elbow might occur, depending on movements of the upper arm and shoulder. Incidental and transient flexor, as well as extensor, movements of this sort occurred continually.

By these and similar methods adaptive flexion and extension of the elbow were achieved without active participation of the test muscles. These movements came to be performed *quite smoothly, so that the monkeys appeared to get along in their natural cage activities without obvious motor impairment*. Such movements tended to obscure whatever action of the test muscles may have been present and, at the same time, reduced the urgency of learning new motor patterns involving the cross innervated muscles.

Besides trick methods of using the elbow passively, many less direct substitutionary reactions were employed, such as increased use of the contralateral arm or of the ipsilateral shoulder and wrist to make up for the defective action of the elbow or use of the mouth, instead of the hands, to pick up food. Many of these substitutionary and trick adjustments probably required no learning at all, whereas others, particularly some of those involving movements of the elbow itself, undoubtedly required practice and learning in varying degrees. Adjustments of the sort described, involving shifts in the function of the normally innervated musculature, constitute the simplest means of readaptation to rearrangement of motor nerves. Even the rat showed some simple readaptation of this kind. The variety and scope of such readjustments, however, were obviously much greater in the monkey.

INHIBITION OF REVERSED MOVEMENTS

Complete readjustment in the action of abnormally innervated muscles requires, first, inhibition of old contraction patterns and, second, positive activation in new patterns. Both may be learned in a single step, or the two may be learned separately. Where learning of the two takes place independently, it is necessary to distinguish between them, because the type of central nervous adjustment may be quite different for the two processes. Undifferentiated inhibition of the arm muscles involves no more difficult an adjustment than would be necessary if the muscles had their normal nerve supply. To inhibit action at the elbow while, at the same time, retaining

movement of the wrist and shoulder is a more complex readjustment and apparently required some practice in the present cases. This still does not involve, however, the more specialized, and presumably more complicated, reversal of relations between the flexors and the extensors, as well as other arm and trunk muscles that would be required for positive readjustment of the contraction phase of the muscles. Also, the ability to halt reversed movements which are already under way ought to be distinguished from the ability to inhibit the initiation of reversed action. The interruption of adverse movements took place readily in most instances, apparently as a result of the visual and kinesthetic effects of the movement in reverse. It is the inhibition of the tendency to start reversed action that required practice and which is the main concern in the following discussion.

Many of the trick reactions mentioned in the foregoing section required that the reversed action of the test muscles be inhibited to permit loose passive movement of the elbow. These trick reactions were learned largely during the period when the test muscles were paralyzed and their active inhibition, therefore, not required. Later, however, when function was restored through reinnervation, active inhibition of the test muscles became necessary. The learning involved in this instance may have been aided considerably by the opportunity to acquire first the positive part of the coordination pattern while the test muscles were still paralyzed.

In some cases it was clear that the monkey learned to inhibit the reversed action of the test muscles rather quickly. For example, the reversed movements in the right arm that appeared immediately after the left arm was rendered useless did not last more than about three or four days in most of the animals. The reversals were most pronounced on the first two days and on the first trials of each test session on succeeding days. In 1 of the spider monkeys clear reversed movements appeared only in the first few attempts to elicit them on the first day and in the first trial on the second day. The animal refused to use the arm thereafter except in performances in which trick movements of various kinds were adequate. In another spider monkey, at the other extreme, the reversals remained conspicuous for about two weeks. The reversed reactions in this exceptional case were eliminated in large part by the end of the first month, but relapses remained common through the succeeding two months. This animal was the one which had had no practice in the use of the arm during the period of nerve regeneration because of temporary paralysis of the muscles of the forearm and hand. The notable difference between this animal and the others indicated that the more rapid inhibition of reversed elbow movement in the other animals could be ascribed to the practice which they had already had in the preceding months, both before and after the reinnervation of the test muscles.

The disappearance of reversed elbow movements after a short learning period under the foregoing conditions does not imply the onset of correct reactions in the test muscles. At first the animals simply refused to employ the arm in circumstances in which it had moved in reverse direction. Later they hesitantly began to use it, gradually dropping out all reversed action at the elbow. This inhibition of reversed action merely made it possible to use the joint passively by various trick methods of the kind described in the preceding section.

In the spécial test situation in which the animals were forced to reach for things through a tube, inhibition of reversed movements came somewhat more slowly. Under these conditions it was not so easy to resort to trick movements, nor was there as much opportunity for practice. In the animal which learned most rapidly it was almost two weeks before the reversed movements were clearly beginning to be inhibited. With most of the animals it was more nearly three to four weeks before they had begun to learn to inhibit reversed action of the elbow in simply reaching for a stationary lure. The reversed action thereafter became less frequent and extensive, but obvious reversals were still not uncommon as late as six, eight, nine and sixteen months after training had been started in different cases. Improvement took place in both arms with about equal speed in 1 of the 3 monkeys with bilateral crossed innervation. In the other 2 monkeys the right arm improved more rapidly than the left, especially in the early stages of training. This was to be expected, for the right arm had recovered first from the operation and had had more practice than the left. The superiority of one side over the other could be taken as evidence either that there was lack of transfer of learning from one side to the other or that the motor coordination used on the two sides was somewhat different.

One spider monkey was exceptional in that it persistently continued to exhibit predominantly reversed action throughout two and one-half years without evidence of any appreciable improvement by learning. This animal was unable to obtain a lure even in a position in which it was merely necessary to relax the test muscles so that the forearm would fall into flexion passively by its own weight. Under these conditions, with the animal obviously straining with full effort to flex the elbow downward, the forearm remained stiffly extended against gravity. Learning appeared abruptly toward the end of the second year of training in this case, and, once started, it proceeded fully as rapidly as in the others. This exceptional monkey was the one in which the left arm was the control. Its slowness in learning may, therefore, have been due to the fact that it used the more proficient control arm regularly and did not give practice to the experimental arm.

The steps by which the different animals learned to reach through a horizontal tube and flex the elbow downward 90 degrees were sur-

prisingly similar, and in some respects not unlike the method of learning described by Weiss and Brown¹¹ after muscle transplantation in man. At first there was only stiff extension of the elbow straight outward against gravity, and after a moment the monkey usually stopped trying to flex the arm and withdrew it from the tube. With sufficient hunger the animal persisted in its efforts for a longer time, in the course of which there were momentary relaxations of the extensor muscles, which may possibly have been accompanied with active contraction of the flexor muscles. In any case, the result was short, sudden flexor movements of the elbow imposed on the predominant extension. These sudden, almost spasmodic, flexor movements were then increased in frequency and extent during the second and third weeks of training, the forearm swinging up and down through an angle of 90 degrees. At the bottom of the downward stroke the hand and fingers came in contact with the lure, but at this stage of learning the hand movements were not coordinated with the elbow movements, and the lure was usually missed because the fingers failed to close at the proper moment. Eventually, after two or three months, the monkey managed to inhibit the predominating extension, so that the forearm, after it had fallen into the flexed position, was not immediately jerked back into extension. There was then time for the fingers and hand to grope for and grasp the lure. At the end of three years the downward flexion of the forearm and the opening and closing of the hand had become coordinated into a single movement, but at best it still lacked in all cases the speed and sureness of the same movement in the control arm.

There was thus a striking difference between the monkey and the rat with respect to the inhibition of reversed movements. In the rat the reversed movements persisted indefinitely. In the monkey, on the contrary, they were quickly halted and inhibited. In only 1 monkey, under particular conditions already described, did the reversal persist in a manner at all resembling that in the rat. This was in an animal which had used its arm comparatively little because of the proficiency of the contralateral arm.

POSITIVE READAPTATION

Readaptation went further than the mere acquisition of various trick movements and inhibition of reversed action. Positive readjustment in the active contraction of the muscles supplied by the crossed nerves was eventually achieved to some degree in all animals. It generally came later and more slowly than inhibition of reversed patterns, although in some reactions the two occurred simultaneously. There was con-

11. Weiss, P., and Brown, P.: Electromyographic Studies on Recoordination of Leg Movements in Poliomyelitis Patients with Transposed Tendons, *Proc. Soc. Exper. Biol. & Med.* **48**:284-287, 1941.

siderable variation in the time required for such readjustments to occur in the various animals and in the level of efficiency finally achieved. Such differences seemed best ascribed to accidents of learning.

Adaptive extension of the elbow against gravity appeared in the right arm of 2 spider monkeys and in the left arm of 1 macaque when they were induced to reach for food in the early months following completion of nerve regeneration. This active extension of the elbow in the correct direction, however, was slow, weak, accompanied with pronounced tremors and generally rather inefficient in all cases. The monkeys were observed to use this extension of the elbow only when food was offered in such a position that it could not be reached otherwise. They preferred to extend the elbow passively and then raise the whole arm from the shoulder whenever possible. Along with these correct extensor actions the animals exhibited as well flexor and extensor movements in reverse in other performances.

When biopsy was performed, it was observed that some extensor fibers had escaped and misregenerated into the extensor muscles in the animals that had first shown adaptive active extension. Similar misregeneration was also observed, however, in 2 other animals which had not shown these early extensor movements. The extent of this unintended reinnervation of the original muscles appeared to be quite small, for only a small twitch of the triceps muscles was elicited with maximum electrical stimulation. In only 1 case was the contraction strong enough to cause a short extensor movement of the elbow. Because the extensor nerves were numerous and some of them very fine, and because the proximal nerve stumps were almost surrounded by extensor muscles, it was difficult to prevent at least a few fibers from escaping back into the extensor muscles. An effort was made at the time of biopsy to search out, cut and ligate all these misregenerated fibers. Afterward, the animals were still able to extend the arm actively at the proper time, however, indicating that by this stage of recovery, at least, the adaptive extension involved function of the nerves successfully crossed. It remained uncertain whether or not the early extensor movements had been effected by the misregenerated nerves.

There was much less chance for the flexor nerves to regenerate back into their proper muscles, and no misregeneration of this sort was seen at biopsy among the experimental animals except in 1 monkey, in which a fine thread of fibers had misregenerated from the median nerve into the brachialis muscle. The function in this case was not significantly different from that in the others. The following data on positive readaptation on the flexor side are, therefore, not complicated by the presence of unintended nerve regeneration.

There was no evidence of active adaptive flexion of the forearm in any of the animals in the course of ordinary cage activities during the

early months following the completion of nerve regeneration. It was not until the monkeys had been trained for varying periods to reach through the tube that the first signs of adaptive flexor action appeared. All the animals eventually learned to flex the forearm against gravity in this situation. At first the flexor movements in the proper direction occurred accidentally and were peculiarly sudden and spasmodic. For example, in an attempt to flex the forearm upward with the upper arm stabilized horizontally in the tube, the predominant reversed extension was occasionally broken by a sudden upward flexion of the forearm, which immediately was snapped back into extension. There seemed to be little or no control over these early accidental movements in the proper direction. Even when the arm flexed sufficiently for the hand to come in contact with the lure, the lure was not grasped. It was as though the correct movement had caught the monkey by surprise, so that it was not prepared to grasp with the hand at that moment. In time the animal learned to grab at the lure at the height of these sudden upward swings. Later still, some control was acquired over the flexion itself, so that the movement could be made more slowly and steadily, allowing time for the wrist, fingers and angle of the forearm to be shifted in adaptation to the particular position of the lure.

In the case of these active flexor movements against gravity, the time required for learning was not appreciably different from that involved in flexion with gravity, where only inhibition was required. By the end of a month the monkeys, with 1 exception, had clearly begun to flex the elbow when flexion was called for, 90 degrees and sometimes more. They were not able to do so consistently and the movements were still rather spasmodic and poorly controlled, but there was unmistakable advancement over the reactions made during the first week of training. The final step to be learned in this performance by most of the animals was the coordination between finger and elbow movements. A point was reached at which the elbow could be flexed properly to bring the hand into the vicinity of the lure and held there, but as soon as the fingers were opened and an attempt was made to grasp the lure, the elbow simultaneously extended, carrying the hand out of reach. By the end of eighteen months this difficulty was overcome. The animals were able to flex the forearm upward to an angle of 90 degrees and to hold the flexed position while the lure was grasped with the fingers. The movements still showed pronounced tremors in 2 monkeys and all the animals had occasional relapses in which the elbow would extend repeatedly when flexion was attempted. In these particular conditions, apparently, the active contraction against gravity was learned about as readily as the downward movement with gravity. With regard to the relative speed of learning on the two sides in the 3 bilateral preparations, the conditions paralleled those already given

for learning to flex the arm downward. Thus, in this respect, also, the learning processes involved in flexing downward with gravity and in flexing upward against it were closely related, suggesting that the coordinations were not much different in the two situations.

The 1 exceptional animal mentioned had not progressed at the end of eighteen months beyond the point where the forearm displayed repeated spasmodic flexions to about 40 degrees at most, with the hand attempting to grasp the lure when it was held within this range. Often the hand failed to close on the lure even when the palm or volar surface of the fingers made contact with it. This was the same animal which had not even learned by this time to relax the brachial muscles so that the forearm could flex downward passively by its own weight. Ability to flex the forearm was acquired suddenly during the second day of a training session near the end of the second year. For the first time the monkey managed to flex the forearm upward a full 90 degrees. The capacity to flex the elbow was retained on immediately succeeding trials in horizontal and downward directions, as well as in the upward direction. In the course of the next two days the flexor movements, which first had been abrupt, spasmodic jerks, became slower and steadier. Positive readaptation in this instance, then, was established directly, without an intermediate stage of indifferent inhibition. As mentioned, this animal in which learning was exceptionally retarded was the one whose other arm served as a control, and it is probable that the delay in learning was causally related to the fact that the experimental arm did not get as much practice as in the other animals.

In the left arm of 2 of the spider monkeys upward flexion of the forearm was conspicuously associated with pronation of the hand. If the hand was in a position of supination, the elbow extended when flexion was attempted. As soon as the hand turned into pronation, the elbow flexed. If the elbow were already in the flexed position and the hand became supinated in an attempt to grasp the lure, the elbow immediately extended, carrying the hand in a reverse direction away from the lure. This association of pronation and supination with flexion and extension of the elbow was rather strict in the first stages of learning but had almost disappeared by the beginning of the third year.

When the lure was moved slowly about with erratic changes in direction after the animal had started to reach for it, the monkey was quite unable to follow it in the early training sessions. Reversed flexor and extensor action at the elbow caused a great deal of excess waving of the arm, with overreaching and false starts, until the monkey either chanced to hit against the lure or ceased trying altogether. Eventually the monkeys all acquired the ability to make their movements predominantly in the correct direction, but complete elimination of reversed action was never achieved in any case. The animal in which the learn-

ing of simple flexion had been exceptionally delayed was greatly retarded in this performance also. Even in the animal with most advanced recovery, the movements after three years remained abnormally slow and hesitant, with pronounced tremors, overreaching and starts in the wrong direction. By contrast, the control arm under similar conditions could immediately snatch a piece of food off the end of the moving stick with no difficulty whatever. Even in simple flexion or extension of the arm to reach a stationary object, there remained to the end an obvious contrast between the quick, sure movements of the control arm and the slow, uncertain movements of the experimental arm.

In their regular cage activities the monkeys continued throughout the three year period of observation to rely primarily on trick methods of using the elbow. However, by the end of two years they had all acquired at least a few movements which involved active participation of the test muscles. For example, in certain positions in which they scratched themselves active elbow flexion against gravity was required. In reaching underneath the cage walls to steal food from neighboring cages, an awkward action in which trick movements were of little help, the animals managed to extend and flex the elbow without aid of gravity. On rare occasions, especially when the animals were competing for food, they would sometimes pick up food and lift it directly to the mouth by flexing the elbow against gravity without bothering to use the knee as a prop. The natural reactions of this kind in which adaptive function of the test muscles was involved were few. Those used most frequently were carried out in a smooth, and apparently automatic, manner without hesitation or tremors, such as were present in the specially trained movements with the tube. The better quality of coordination in these common cage activities may be attributed to the much greater amount of practice which they received. Vision was used to help guide the elbow movements to a large degree, but it was not necessary. The scratching reactions were regularly carried out without visual aid. Also, in reaching through the tube, it was common for the monkeys, after locating the position of the lure visually, to turn the head sideways in the act of reaching, so that the eyes could not be used further in guiding the arm movements.

GENERALIZATION AND TRANSFER OF LEARNED REACTIONS

It is theoretically conceivable that, having once learned in a particular performance to flex the elbow with cross innervated muscles, the animal might thereafter be able to flex the elbow properly in any other performance. On the other hand, it is possible that flexion and extension of the elbow would have to be relearned separately for each performance. The actual results came much nearer the latter extreme than the former. There were a number of instances in which the learning

clearly failed to be transferred spontaneously from one performance to another. For example, after animals had learned to inhibit reversed flexion when trying to extend the arm horizontally for food in front of the cage, they again exhibited reversed flexion when induced to reach under similar conditions through the side of the cage or from a height or posture different from that in which the original learning had occurred. Most of the animals had learned to inhibit reversed action of the test muscles before they were tested with the tube. When these tests were started, however, the same reversal of elbow movement reappeared, and its inhibition had to be learned again in the new situation. The animal which was exceptionally slow in learning to flex the elbow when reaching through the tube had been able to flex the elbow to scratch itself or to pull food through the cage wires for almost a year before it finally learned to flex the elbow similarly in the tube situation. There was, thus, a striking lack of transfer in many instances.

If the learning process involved rearrangements in the relationships, of the primary or secondary neurons with the spinal centers, as contended at times in the past, one would expect a complete transfer of learning from one performance to all. Once the basic relationships of the spinal limb centers had been readjusted, the adjustment should be effective for all limb movements. The fact that learning to flex or to extend the elbow in one situation did not necessarily become generalized for other performances indicated that the neural readjustment was not localized in the spinal centers but involved, instead, reorganization of cerebral processes specialized for the different performances.

EFFECT OF PENTOBARBITAL AND CORTICAL LESIONS

To see whether it would cause a breakdown in the new coordination patterns and a return of reversed movement, 2 of the animals were given a three-fourths anesthetic dose of pentobarbital sodium subcutaneously. This was done on two separate occasions near the end of the third year. When the monkeys had reached a stage at which they were beginning to be unsteady in their movements, the elbow coordinations were tested. In 1 case there was a definite increase in the amount of reversed action at the elbow, but not a complete breakdown of the adaptive movements. It looked as though the animal was quite indifferent, and not concentrating on the arm movement as much as usual. In the second case the drug seemed to improve the elbow coordination. Under the influence of pentobarbital, this animal used the elbow more frequently than usual and with less tension. The animal seemed to be better relaxed, and the arm did not show the stiff extension which characteristically occurred under normal training conditions when flexion was attempted. This animal was the exceptionally slow learner. Apparently, the relaxation produced by pentobarbital may have either a bene-

ficial or a deleterious effect, depending on whether the animal in normal circumstances is sufficiently or too little relaxed for optimal performance.

An attempt was also made to produce a relapse into reversed movements by making lesions in the cerebral cortex. In 1 animal bilateral destruction of arm area 6 and the anterior half of arm area 4, as given on architectonic charts, caused so severe a paralysis that meaningful tests could not be made. In 2 additional animals the frontal lobes were removed bilaterally, and in another operation extensive lesions were made in postcentral arm areas 1, 2, 5 and 7. In 1 of these animals the frontal lobes were removed first, and in the other the postcentral lesions were made first. In both animals the removal of the frontal lobes produced a temporary increase in the amount of reversed action, from which there was recovery by the end of two weeks. The postcentral lesions made it difficult for the monkeys to aim the arm movements accurately. They had great difficulty, for example, in getting the hand into the tube. In the flexor-extensor movement of the elbow, however, there was no sign of increased reversal. The results showed that the habit was not dependent on the frontal lobes and suggested that kinesthetic stimuli from the arm were not of major importance in the control of the adapted elbow coordinations.

ANATOMIC CHECKS

When the animals were killed, the brachial nerves were dissected free, with the use of anesthesia, and stimulated electrically to test for the presence of nerve fibers innervating their original muscles. All animals seemed to be free of such fibers except for the control monkey. Apparently, all unintended regeneration that had been present was successfully eliminated in the biopsies earlier in the experiments. The brachialis muscle in 1 of the macaques was not completely atrophic but did not contract to stimulation of any of the flexor nerve trunks. In the right arm of 1 of the spider monkeys the triceps muscles were not more than one-eighth their normal size. In the left arm of another spider monkey only the medial head of the triceps muscle was reinnervated, the other parts being atrophic. The test muscles were otherwise in good condition and ranged roughly from about two-thirds normal to normal in size. Stimulation of the nerves proximal to the region of cross union produced quick, vigorous responses of the forearm in the direction opposite the normal. Further dissection of the nerves disclosed nicely crossed nerve connections with no further evidence of unintended regeneration. Microscopic examination of samples of the crossed nerves from 3 of the animals showed rich reinnervation of the distal nerve stumps. In the region of the scar the fibers followed rather erratic courses, but this was not of much consequence because the motor components of the nerves were functionally homogeneous.

COMMENT

When the foregoing results are compared with those obtained after the interchange of limb nerves in the rat, the superior readaptive capacity of the monkey is very apparent. The monkey is quick to halt reversed movements, as well as to find new ways of accomplishing various acts without using the abnormally innervated muscles. Positive correction in the contraction phase of the test muscles was also eventually achieved. The active coordination of the cross innervated muscles became smooth and automatic in the course of two years in some reactions which received constant daily practice in regular cage activities. The rat, on the other hand, was found to repeat the reversed movements indefinitely without correction and even without inhibition of the reversed action.

Regarding the problem of the neurologic basis of the monkey's superiority, there are a number of known factors that appear significant. First, there are the obvious advancements in the structure of the primate nervous system and its associated end organs,¹² of which the following may be listed as particularly pertinent: (*a*) the more highly developed sensorimotor cortex; (*b*) the more elaborate connection systems between the spinal limb centers and the higher levels of the brain, especially the corticospinal tracts and the dorsal funiculi and medial lemniscus system; (*c*) the increased ratio of sensory to motor fibers in the limb nerves; (*d*) the increase in number and differentiation of sensory nerve terminations in the skin, tendons, muscles and joints, and (*e*) the mechanical arrangement of the muscles and skeleton of the primate limb so as to permit a much greater range of variation in limb movements than is possible in the rat.

To these anatomic differences may be added a number of functional differences which showed up in the course of the experiments. First, the monkey appears to have a greater capacity for detecting the presence of abnormal movements and for sensing in some degree the location and nature of the motor difficulty. Whereas the rat may continue indefinitely to repeat without modification a movement in reverse and seems meanwhile to remain oblivious of the reversed action, the monkey indicates by its behavior a more direct awareness of when and where an error has been made. The beginning of a single movement in reverse is often sufficient in the monkey to disrupt the activity going on at the moment. Sometimes it appears that the monkey stops and concentrates its attention on the member that is at fault. This is particularly true

12. Ariëns Kappers, C. U.; Huber, A. C., and Crosby, E. C.: *The Comparative Anatomy of the Nervous System of Vertebrates, Including Man*, New York, The Macmillan Company, 1936.

when the limb is being used in a "voluntary" manner, as in reaching for or handling something.

This difference in capacity for perceiving the presence and location of adverse reactions is correlated with a second factor, namely, a difference in the way the animals naturally use their limbs. The rat is not adapted, like the monkey, for finely controlled, deliberate, delicate movements of individual limbs or separate segments of the limbs, as in manipulation. It is in movement of this sort that learning appears to occur most readily. Both the aforementioned factors are therefore probably important in the monkey's superiority: the ability to make discriminate voluntary movements of individual limbs and parts of the limb, and also the perceptual capacity to attend to such specific movements, to guide them and to note their effects.

There is a third possible factor, not unrelated to the two already indicated, which may also account in part for the monkey's quicker detection and inhibition of reversed movements, namely, a greater dependence of the motor control of limb movement on sensory cues, especially those originating within the limb itself. In the rat the adverse sensory effects resulting from movement of one joint in reverse is not sufficient, as in the monkey, to disrupt the motor sequence. The aforementioned three factors together make the reversed action of cross innervated muscles inconspicuous in the monkey as compared with the rat.

Another factor of significance is the greater diversity of limb movement present normally in the monkey. The rat tends to use a limb as a whole in a stereotyped manner, with relatively few variations of the coordination pattern. In the monkey, however, the various limb segments may act differentially, being flexed, extended or rotated in various combinations, with a large variety of possible permutations of the coordination pattern. Because dissociation in the action of cross innervated muscles is a prerequisite of readaptation, the monkey, with a high degree of such functional dissociation already present normally, has a great advantage over the rat, in which the limb muscles are more rigidly bound together in restricted functional associations.

The ability to activate the test muscles in many different combinations with other limb muscles opens the possibility for their activation in the new proper combination to suit the crossed innervation. It is necessary in learning a new motor skill to achieve the new coordination a first time, whether by directed effort or by accidental blunder. Once made, the new coordination can be reenforced by further repetition and practice. In the rat the proper coordination was apparently never achieved, even a single time. The limb always worked in the old patterns, without any trial variations. It remained questionable whether the motor system of the rodent is so organized as ever to permit the

required reassociation of muscle function. The ability of the monkey to make diversified trial coordinations would seem to be an extremely important item.

Another factor favoring motor reeducation in the monkey is the fact that learning plays a much greater role in the original ontogenetic acquisition of motor coordinations. The monkey to start with is, therefore, already more experienced than the rat in learning new arm coordinations. Furthermore, it is to be expected that coordinations established largely by learning in the first place will be more easily reorganized by the learning process than those built into the system by processes of growth and maturation.

In addition to the specific items aforementioned, there remains supposedly a central intelligence factor involving the general organization and differentiation of the brain, regarding which little can be added on the basis of the present experiments.

The foregoing advancements ascribed to the monkey are, of course, to be found also in man, even better developed in most instances. Certainly, man would be far superior to the monkey in the early stages of reeducation, i. e., in the detection and understanding of the motor difficulty and, consequently, in the guidance of corrective training. In any attempt to extrapolate to man from these results in the monkey, one must remember that most of the cases of nerve crossing and nerve regeneration, as well as those of muscle transposition, met in the clinics require a different and more complicated type of motor reorganization than that demanded by the clearcut reciprocal cross of these experiments.

SUMMARY

1. In 4 spider monkeys (3 with bilateral and 1 with unilateral crossed innervation) and in 2 macaques (both with unilateral crossed innervation) reversed movements of the elbow followed the surgical interchange of the nerve connections of the elbow flexor and extensor muscles with removal of all other muscles acting on the joint.

2. These reversed movements were quickly abandoned in ordinary cage activities, and a large variety of "trick" or compensatory reactions were rapidly acquired as substitutes for the abnormal action of the test muscles.

3. After about two months' practice at most, the reversed movements could be elicited only by using special measures to force the animals to use the elbow under conditions in which trick movements were excluded and in which there had not been previous opportunity to learn to inhibit the reversed action.

4. Readaptation went farther than the development of trick movements and inhibition of reversed action. Positive readjustment in the

function of the test muscles was eventually achieved in all cases, until the monkeys could actively flex and extend the elbow in an adaptive manner. A few of these corrected reactions which received constant practice in natural cage activities seemed to be as smoothly coordinated at the end of three years as the same movements in a control case after a similar operation but in which the nerves regenerated into their original muscle groups.

5. Correct use of the cross innervated muscles learned in one performance was not transferred automatically to all other performances. Lack of such transfer was strikingly apparent in a number of instances.

6. Reversed action at the elbow persisted throughout the three year course of the experiments in certain performances which received comparatively little practice.

7. The new motor coordinations survived bilateral frontal lobectomy combined with extensive bilateral lesions in the cortical arm areas 1, 2, 5 and 7.

8. Comparison of the present results with those of similar surgical operations carried out previously on the rat indicated throughout a marked superiority of the monkey. Some of the known factors, anatomic and functional, contributing to this readaptive supremacy of the primate nervous system are discussed.

Department of Anatomy, the University of Chicago.

INNERVATION OF THE CHOROID PLEXUS

MARIA TSUKER

MOSCOW, UNITED SOVIET SOCIALIST REPUBLICS

THE STUDY of the innervation of the choroid plexus is attended with great technical difficulties, explaining the paucity of investigations on this subject. Isolated notes on the nerve supply of the choroid plexus are found in the works of older authors. As far back as 1874 Benedikt¹ identified nerve fibers in the choroid plexus of the fourth ventricle. He used carmine staining. These fibers were rami of the tenth nerve and originated in the cells of the nucleus ambiguus. Benedikt named these fibers "the thirteenth nerve." His observations were confirmed by Bokhdallek and Purkinje. Bkhnenek described nerve plexuses around the vessels of the "paraphysis" of the frog. He was able to trace the course of the fibers from these plexuses to the choroid plexus of the lateral ventricles. Findley drew attention to the presence of sympathetic nerve fibers in the choroid plexus of man and cattle. Together with Studnitska, he discovered ganglionic structure in the choroid plexus. According to Findley, the sympathetic fibers of the choroid plexus arise from the internal carotid plexus, and he denied the possibility of a different origin.

SURVEY OF LITERATURE

In 1911, Khvorostukhin, by using a methylene blue stain, discovered in the choroid plexus of various mammals nerve plexuses consisting of thick medullated and thin nonmedullated fibers. He was able also to trace the branching from thick nerve fascicles of thinner fibers, from which, in turn, still thinner fibers branched off. Subepithelial plexuses of thin nerve fibers were also identified by Khvorostukhin. In exquisitely stained slides, he observed how rami of a subepithelial plexus gave off thin nerve fibrils, which terminated on the surface of the epithelial cells. Finally, he discovered nerve fibers and their plexuses around blood vessels.

Stöhr² described the innervation of the cerebral membranes and made accurate notes on the innervation of the choroid plexus. He made

1. Benedikt, M.: Ueber die Innervation des Plexus choroideus inferior, Virchows Arch. f. path. Anat. 59:395-400, 1874. .

2. Stöhr, P.: Ueber die Innervation des Plexus choroideus des Menschen, Ztschr. f. d. ges. Anat. (Abt. 1) 63:562-607, 1922.

his studies on fresh human material, using a modified Schulze staining method (Schulze-Stöhr technic). He discovered a great many nerve fibers in the choroid plexus and the tela choroidea and divided them into two groups—the vascular nerves and the nerves of the plexus (*nervi propii*). According to Stöhr, the innervation of the choroid plexus, especially its blood vessels, strongly resembles the innervation of the leptomeninges. There are nerve fibers attached to the blood vessels of all calibers in the choroid plexus as well as in the leptomeninges. Stöhr called these fibers vascular nerves. The nerve fibers not directly participating in the vascular innervation he referred to as *nervi propii*. Particularly ample is the nerve supply of the tela choroidea of the third and fourth ventricles. In this structure there are tiny fascicles of non-medullated fibers, as well as dense plexuses of very thin fibrils. In the tela choroidea of the third ventricle Stöhr saw thickened, pear-shaped nerve endings. In these terminal bulbs the nerve fibers either form tiny fibrillary networks or end in minute terminal knobs. Stöhr assumed that these two types of nerve terminations have the character of afferent nerves. He described the origin of the nerve fibers of the choroid plexus as follows: The nerve fibers proper of the choroid plexus of the fourth ventricle arise in the nucleus of the tenth nerve, in the pons varolii and in the pedunculi cerebri. Nerve fibers from the brain substance itself enter into the plexus choroideus which overlies the thalamus. The tela choroidea of the third ventricle receives nerve fibers directly from the striae medullares. Stöhr confirmed the opinion of other authors that the sympathetic fibers of the leptomeninges and of the choroid plexus arise from the internal carotid and the vertebral plexus. However, neither Stöhr nor the others demonstrated the origin of the nerves of the choroid plexus by special technics or by experiments.

Junet³ fixed the plexus choroideus of a mouse *in toto* by the method of Stöhr and identified a perivascular nerve plexus and fascicles of nerve fibers in the stroma of connective tissue. He also described sub-epithelial nerve plexuses and tiny fibrils which entered the epithelial cells. These fibrils often terminated in little whirls.

Clark⁴ studied the innervation of the fourth ventricle. His experimental animals consisted of cat embryos and newborn and young cats, as well as dogs, rats and rabbits. He used Ranson's staining method with pyridine and silver. He established a difference in the innervation of the lateral and that of the medial portion of the choroid plexus. He stated the belief that innervation of the lateral portion resembled the innervation of the cerebral membranes, as described by Stöhr. The

3. Junet, W.: A propos d'un plexus choroïde justa-hypophysaire chez l'*Uromastix acanthinurus* (Bell), *Compt. rend. Soc. de biol.* **97**:556 (July 22) 1927.

4. Clark, S. L.: Nerve Endings in the Choroid Plexus of the Fourth Ventricle, *J. Comp. Neurol.* **47**:1-21 (Dec.) 1928.

nerves of the lateral part of the plexus of the fourth ventricle had a twofold source. Some accompanied the vessels, whereas others originated in the dorsolateral area of the medulla oblongata and formed a fascicle, referred to as the "thirteenth nerve" by Benedikt. The nerve fibers of the medial portion originated in the substance of the medulla oblongata and joined the choroid plexus by way of the taeniae acusticae. The nerves of the plexus choroideus of the fourth ventricle showed well defined terminations, the type of which reminded one of sensory nerve endings.

In his studies on the innervation of the meninges of man at the level of the medulla oblongata, Snessareff concentrated his attention on the tela choroidea. In the tela choroidea of the fourth ventricle both solitary fibers and small fascicles of nonmedullated and medullated nerve fibers are present. Many of the nerve fibers characteristic of the tela choroidea are distinguished by certain peculiarities. They spread out under the epithelium without forming the fascicles or plexuses so characteristic of the meninges. These fibers are nonmedullated, show few varicosities and lack the cells of Schwann. In the choroid plexus of the fourth ventricle, besides vascular nerve fibers, others of the terminal type were discovered by Snessareff, the ramifications of which surrounded the epithelial cells like a network. The author did not agree with Stöhr's division of the nerve fibers into vascular and proper nerves; he suggested, rather, that the former be defined as a nerve-plexus of the vascular walls and the latter as an intervascular plexus.

Shapiro⁵ did research on the innervation of the choroid plexus of man and various mammals. Fresh material was used, never older than twelve hours. She employed the silver staining methods of Ramón y Cajal, Bielschowsky, Gros-Bielschowsky, Schulze and Stöhr and the old and new methods of Golgi. She drew attention to the great technical difficulties, explained by the impossibility of making frozen sections and by the presence of numerous salts and amyloid and hyaline corpuscles in the tissues. The best results were obtained with the Schulze-Stöhr staining method. Shapiro observed that the choroid plexus was rich in nerve fibers. Fascicles of various calibers contained nonmedullated and medullated nerve fibers. She also saw thick medullated fibers with distinct nodes of Ranvier. The thick bundles of nerve fibers broke up into thinner bundles, from which still thinner bundles were separated, and the latter finally split up into single nerve fibrils. In some of the nerve fibers varicose turgescences and characteristic triangular swellings were present at the sites of ramification. Occasionally, also, dichotomous divisions of the fibers were seen. Single nerve fibers might cross, forming a network of fibers. In the cluster-like portion of the choroid plexus fascicles were absent. The author was able to trace the penetration into

5. Shapiro, B.: Ueber die Innervation des Plexus choroideus, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:539-546, 1931.

the epithelium of tiny varicose nerve fibrils and their termination between the epithelial cells. There were also thicker medullated nerve fibers in the clusters. Shapiro emphasized that the epithelium of the choroid plexus is scantily supplied with nerve fibers.

MATERIAL AND METHODS

My associates and I studied the innervation of the choroid plexus in dogs and cats. The animals were killed by applying an electric current to the heart. The brain was removed four to six hours after death. Immediately thereafter, or within the next hour, the choroid plexus was extirpated and placed in "A F A" or in neutral solution of formaldehyde U. S. P. ("A F A," used by Lavrentieff, consists of equal parts of 96 per cent alcohol, neutral solution of formaldehyde U. S. P. and a 1 per cent solution of arsenic acid). The hardened choroid plexus was then stained as a whole, without being sectioned. Various silver stains were employed, the Gros-Bielschowsky method yielding the best results. The other silver stains proved unsatisfactory for our material. The stained specimens were affixed to glass plates with albumin-glycerin solution, smoothed out with a glass rod and covered with Canada balsam.

Our specimens showed an ample nerve supply of the vascular plexus of all ventricles. The nerve fibers were scattered in the stroma, around the vessels and subepithelially in the clusters of the choroid plexus. The nerve fibers throughout the connective tissue stroma of the choroid plexus varied slightly in number and distribution from those in its racemose portion. In conformity with other authors, we refer to the nerve fibers surrounding the vessels as vascular nerves. We suggest the name stromal nerves for the nerve fibers scattered through the connective tissue. This term seems to us plainer and more appropriate than the term applied by Stöhr (proper) and that used by Snessareff (intervascular). The nerve fibers run from the vessels of the choroid plexus into the surrounding tissues, whereas from the stroma they take their course to the vessels. This variable course of the nerve fibers makes the classification into two groups appear somewhat schematic and conventional. We noted in the choroid plexus both medullated and nonmedullated fibers, the latter being in the majority. Many fibers showed a rosary-like appearance, indicating their sympathetic origin. In the connective tissue stroma of the choroid plexus fascicles of varying caliber were seen. From the thicker bundles thinner ones branched off, which, in turn, split up into still thinner bundles and, finally, into solitary fibers. The thinnest bundles branched off from the more massive bundles at varying angles. The division of the thin bundles into thinner bundles and into solitary fibers was brought about by dichotomous division, seldom by ramification. At the sites of bifurcation and trifurcation of the nerve fibers the protoplasm became denser and took on a triangular shape (fig. 1 *A* to *F*, inclusive, and *H*; fig. 2 *A* and *B*). The greatest number of massive nerve bundles were observed in the connective tissue stroma of the choroid plexus of the lateral ventricles

Many nerve bundles ran parallel with the fibers of the stroma itself. Some bundles were tortuous, forming knees or other figures, communicated with each other and were plaited together into networks. Such networks might be composed of the fibers of but one bundle. The nerve fibers of the stroma frequently passed over to the vessels, uniting with the vascular nerves. On many slides single nerve fibers were seen, which ended freely in terminal thickenings, resembling little knobs, trowels, spirals or nooses. Such nerve terminations were present in the stroma, as well as around the vessels. The vessels of the choroid plexus of all ventricles were amply supplied with nerve fibers around the adventitia. These fibers were arranged in the longitudinal axis of the vessel, though they often cut athwart the vessel and formed networks and plexuses on its wall. Nerve fibers, of various calibers, were encountered around the vessels. Here and there nerve fibers ran from the vascular walls into the surrounding tissue. Each cluster of the choroid plexus of all the ventricles possessed a subepithelial network of very fine nerve fibers. Either the fibers approached the epithelial cells, ending in knoblike turgescences, or their terminations lay on the very surface of the cells, extending sometimes as far as their nuclei (fig. 1 *G* and *I*). Owing to the technical difficulties of staining, the subepithelial nerve plexuses and the approach of the fibers to the epithelial cells were not visible in all specimens. The tela choroidea of the third and fourth ventricles showed the well known peculiarities of innervation. It was provided with a multiplicity of very fine nerve fibers, running in diverse directions. These fibers, communicating with one another, formed delicate interlacings and networks. There were rosary-like turgescences in many of the nerve fibers. Some solitary fibers ended on the epithelial cells that overlie the tela choroidea. The nerve terminations were analogous in type to the terminations on the epithelial cells of the clusters of the choroid plexus, as previously described.

We did not detect any massive bundles of nerve fibers in the tela choroidea. In none of our preparations were nerve cells observed.

In the experimental part of this work we tried to confirm the assumption of several authors that a known part of the nerve fibers of the choroid plexus originates in the nerve networks of the vessels supplying the choroid plexus. As is well known, the choroid plexuses of the lateral ventricles receive their blood supply from the anterior choroid artery, a branch of the internal carotid artery, and from the posterior choroid artery, a branch of the posterior cerebral artery. For the denervation of the internal carotid artery and its branch, the anterior choroid artery, we removed the superior cervical (sympathetic) ganglion on one side (on the right side). This experiment was performed on cats and dogs. The removal of the superior cervical ganglion was carried out in 19 dogs and cats, but a satisfactory staining of the nerves

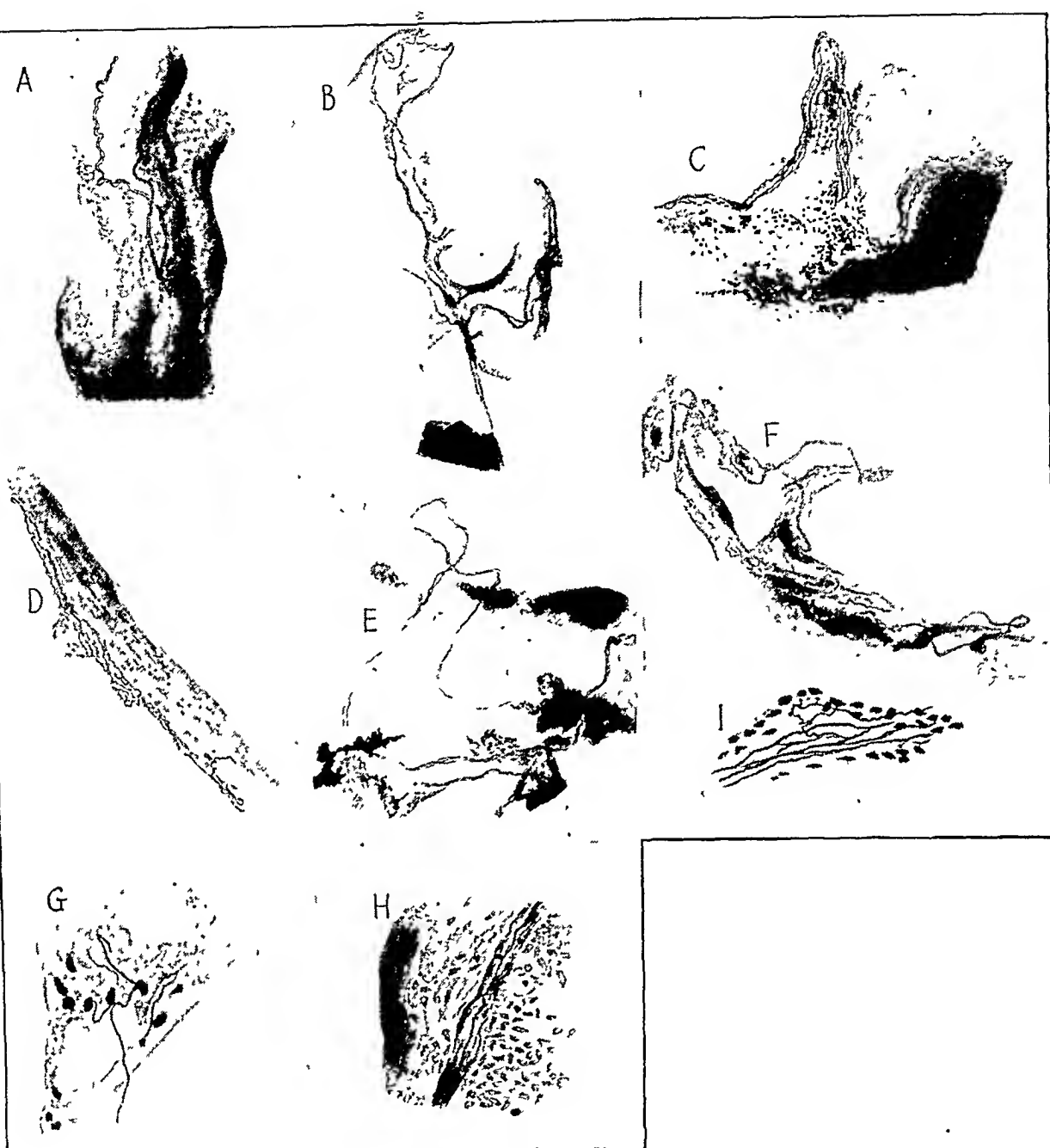


Fig. 1.—*A* (preparation 9; Gros-Bielschowsky stain), nerve fibers in the connective tissue (vascular plexus of the lateral ventricle of a cat). *B* (preparation 9; Gros-Bielschowsky stain), bundles of nerve fibers in the connective tissue (vascular plexus of the lateral ventricle of a cat). One of the bundles passes over into the cluster-like portion. *C* (preparation 9; Gros-Bielschowsky stain), distribution of nerve fibers on the border of connective tissue (vascular plexus of the lateral ventricle of a cat). *D* (preparation 10; Gros-Bielschowsky stain), nerve fibers in a cluster-shaped portion (vascular plexus of the fourth ventricle of a dog). *E* (preparation 7; Gros-Bielschowsky stain), nerve fibers in the connective tissue (vascular plexus in the lateral ventricle of a cat). *F* (preparation 6; Gros-Bielschowsky stain), course and distribution of nerve bundles in the connective tissue (vascular plexus of the lateral ventricle of a dog). *G* (preparation 14; Schulze-Stöhr stain; $\times 400$), termination of nerve fibers on epithelial cells (vascular plexus of the lateral ventricle of a cat). *H* (preparation 1; Gros-Bielschowsky stain; $\times 400$), bundle nerve fibers, spreading along vessels (vascular plexus of the third ventricle of a cat). *I* (specimen 18; Schulze-Stöhr stain; $\times 400$), nerve fibers inside cluster and nerve terminations on epithelial cells (vascular plexus of the lateral ventricle of a cat).

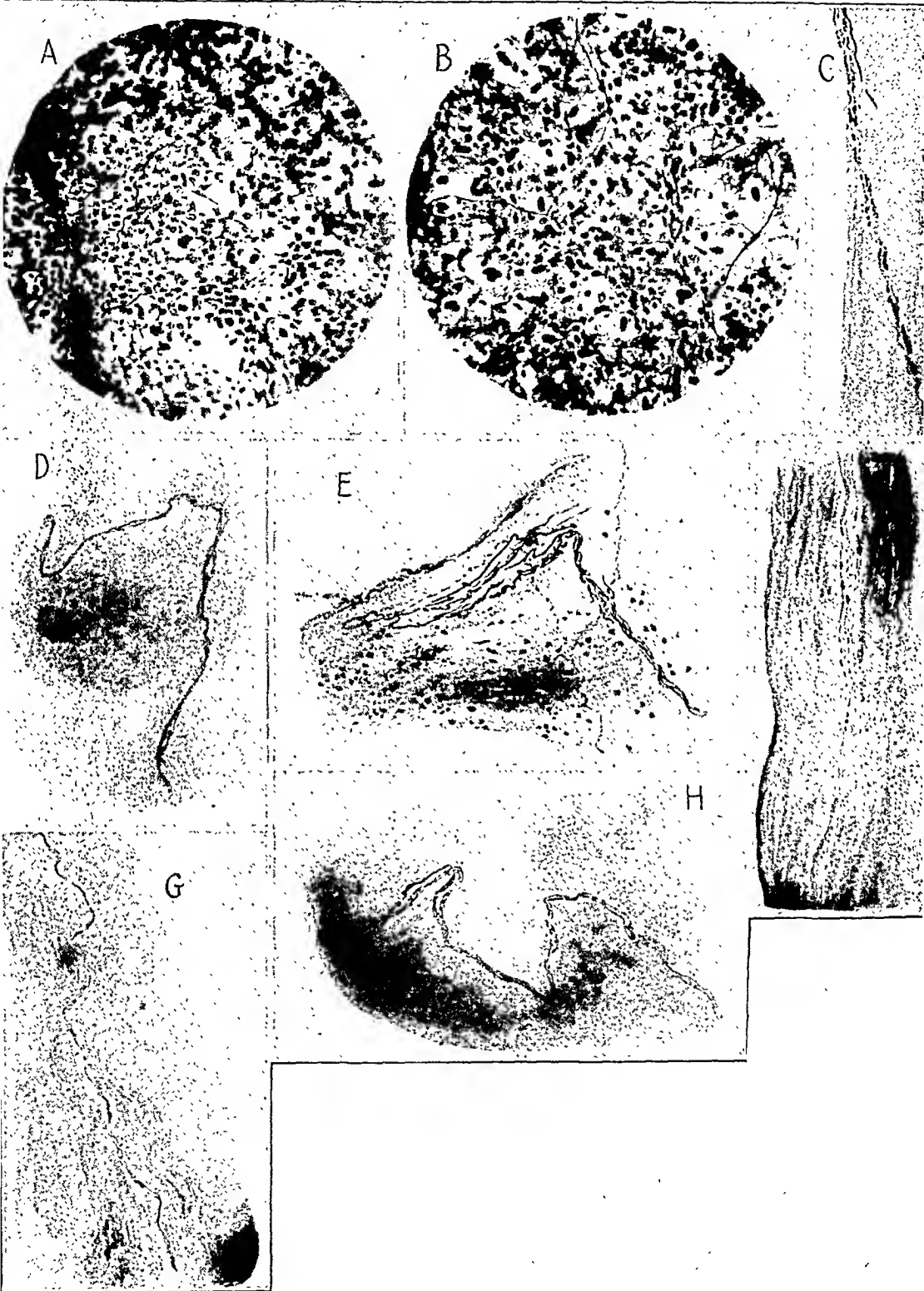


Fig. 2.—*A* (preparation 19; Gros-Bielschowsky stain), thin nerve fibers with their network, dense protoplasm, bifurcations and trifurcations at sites of division of fibers (tela choroidea of the third ventricle of a cat). *B* (preparation 19; Gros-Bielschowsky stain), thin nerve fibers, many of them with a rosary-like appear-

(Legend continued on next page)

of the vascular plexus was obtained in only 13 animals. By the unilateral removal of the sympathetic ganglion we were able to compare the innervation of the choroid plexus of the lateral ventricle on the side of the extirpated ganglion with the innervation of the normal plexus.

The staining of the nerve fibers of the choroid plexus from the right lateral ventricle yielded good results in 9 animals, while the staining of the corresponding structures from the left ventricle turned out well in 8 animals. The nerve fibers of the choroid plexus from the third ventricle stained well in 10 animals. The signs of degeneration of the nerve fibers were argentophilia, fragmentation, complete disintegration and disappearance of the axis-cylinders. We observed them in 7 out of 9 stained vascular plexuses of the right lateral ventricle, i. e., on the side on which the superior cervical ganglion had been extirpated. These changes apply to argentophilia, fragmentation and the breaking up of axis-cylinders into the smallest particles, leaving behind the empty nerve sheaths (fig. 2 *C* to *H*, inclusive). Such changes were seen only in single fibers and in a few fiber bundles. The pathologic nerve fibers lay in the stroma and around the vessels. The main portion of the nerve fibers in the corresponding controls showed normal structures. It is noteworthy that in no slide bearing the choroid plexus of the left lateral ventricle, i. e., the ventricle on the normal side, were degenerations of nerve fibers traceable.

These findings suggest that with the removal of the superior cervical ganglion there develops in the choroid plexus of the homolateral lateral ventricle a degeneration of single nerve fibers and their bundles lying in the stroma of the network and around the vessels, whereas the major portion of the nerve fibers of this plexus remain intact. Evidence of degeneration exists sometimes forty-eight hours after the extirpation of the ganglion. As to the exact time of the appearance of the greatest structural changes, no definite conclusions could be derived from our material.

ance (turgescences) (tela choroidea of the third ventricle of a cat). *C* (preparation 15; Gros-Bielschowsky stain), coarse disintegration of axis-cylinders into single minute particles (vascular plexus of the right ventricle of cat 8). *D* (preparation 48; Gros-Bielschowsky stain); degeneration of nerve fibers, disappearance of axis-cylinders, empty nerve sheaths (vascular plexus of the third ventricle of cat 28). *E* (preparation 59; Schulze-Stöhr stain), degeneration of nerve fibers, disintegration of axis-cylinders, regrowth and thickening of nerve fibers (vascular plexus of the left ventricle of a dog; in this dog, "Zhuchka," the superior cervical ganglion on the left side had been removed). *F* (preparation 40; Gros-Bielschowsky stain), marked disintegration of nerve fibers and fragmentation (vascular plexus of the third ventricle of cat 17). *G* (preparation 1; Gros-Bielschowsky stain), disintegration of nerve fibers, absence of axis-cylinders, empty sheaths, Schwann cells (vascular plexus of the right ventricle of cat 3). *H* (preparation 1; Gros-Bielschowsky stain), marked disintegration and partial disappearance of axis-cylinders. Here and there are empty sheaths (vascular plexus of the right lateral ventricle of cat 3).

Five out of 10 stained plexuses of the third ventricle showed degeneration of part of the nerve fibers. The histologic changes resembled those seen in the plexus of the right lateral ventricle. Numerically, the changes in the fibers were few. In the specimens showing degenerative changes the majority of nerve fibers had retained their normal appearance. In the choroid plexus of the remaining 5 animals no structural changes of the nerve fibers were noted. This demonstrates that the extirpation of the superior cervical ganglion can produce degeneration of single nerve fibers of the choroid plexus of the third ventricle.

COMMENT

Our experimental observations prove that part of the nerve fibers of the choroid plexus of the lateral ventricle are derived from the network of nerves surrounding the branches of the internal carotid artery. The main artery supplying the choroid plexus of the lateral ventricle is the anterior choroid artery, a branch of the internal carotid artery, which receives its nerve fibers from the network of the internal carotid artery. The innervation of the internal carotid artery is mainly, though not exclusively, made up of sympathetic fibers from the superior cervical ganglion. The degeneration of part of the nerve fibers belonging to the plexus of the lateral ventricle after the extirpation of the superior cervical ganglion is explained by the fact that these fibers run to the choroid plexus conjointly with the anterior choroid artery; i. e., they are extensions of the plexus fibers of the internal carotid artery. As previously stated, we noticed degenerative processes in only a few of the nerve fibers, whereas the major portion remained intact. We interpret this in the following way: First, the extirpation of the ganglion does not lead to complete denervation of the internal carotid artery, and, consequently, it cannot cause a complete denervation of its branches, to which the anterior choroid artery belongs. Second, one must take into account that the choroid plexus of the lateral ventricles is supplied with blood also from the posterior choroid artery, which is a branch of the posterior cerebral artery, and that part of the nerve fibers doubtless run to the choroid plexus conjointly with this artery. Third, one may reasonably conjecture that not all nerve fibers of the choroid plexus of the lateral ventricles are derived from nerve networks of blood vessels supplying the choroid plexus. Degeneration of nerve fibers in the choroid plexus of the third ventricle was seen only in half the specimens, indicating that one was not dealing with a constant feature, such as was present in the plexus of the lateral ventricle on the side of extirpation of the ganglion. The choroid plexus of the third ventricle receives its blood supply from the branches of both internal carotid arteries. This special blood supply of the plexus of the third ventricle probably accounts for the inconstant appearance of degeneration of nerve fibers after the

unilateral extirpation of the superior cervical ganglion. With regard to the innervation of the choroid plexus of the third ventricle, it is a logical assumption that not all nerve fibers of this structure come from the nerve networks of the vessels supplying the choroid plexus.

CONCLUSIONS

The results of our experiments with extirpation of the superior cervical ganglion confirm the theory of other investigators, according to which part of the nerve fibers of the choroid plexus originate from the nerve network of the blood vessels supplying the plexus. Our results, further, prove that the origin of certain portions of the nerve fibers belonging to the choroid plexus of the lateral ventricles, and, to a minor degree, of the corresponding structures of the third ventricle, lies in the nerve networks of branches of the internal carotid artery, springing from the superior cervical ganglion. Finally, our observations give evidence that in all probability not all nerve fibers of the choroid plexus originate from the nerve networks of the arteries.

Neurological Department, First Moscow Medical Institute.

CLINICOPATHOLOGIC ASPECTS OF PARKINSONIAN STATES

Review of the Literature

JAMES W. HEATH, M.D.*

NEW YORK

THE DIVERSITY of opinion surrounding (1) the minimal pathologic substrate of the parkinsonian syndrome and (2) the correlation between specific pathologic changes and component parts of the syndrome is well known. A new review of the literature of the clinicopathologic aspects of parkinsonism was accordingly undertaken to determine whether a comprehensive survey of this material would serve to clarify these matters.

In order to make the problem clear, it may be observed that, while a particular series of cases often suggest definite clinicopathologic correlations, these correlations are exceedingly difficult to substantiate when one examines a large number of differently reported series of cases. The following cases briefly illustrate various incompatibilities.

VARIATIONS IN THE PARKINSONIAN STATE WITH ILLUSTRATIVE CASES

Tremor.—Tremor may appear either on the same or on the opposite side of greatest damage of the substantia nigra or may be absent even though this structure is seriously damaged.

CASE 3 (Benda and Cobb¹).—*History and Examination.*—A man aged 60 entered the hospital with the chief complaint of weakness and tremor of the left hand. About one year prior to admission he first noted tremor of the left hand, which occurred when the hand was at rest. The tremor spread to the elbow. Just before his admission to the hospital weakness developed in the feet, the weakness being more pronounced on the left side. The patient tended to hold his body slightly flexed. The reflexes were reported to be normal. Rigidity was not mentioned in the report.

Microscopic Study.—On the whole, the cells of the basal ganglia and the subthalamic region were well preserved. Demyelination of the globus pallidus was pronounced bilaterally.

The most outstanding change was in the substantia nigra, which showed loss of cells in the lateral area on both sides, the area of the right side being only two-thirds that of the left. The fibers of the substantia nigra showed definite demyelina-

*Dr. Heath is now at the University of Mississippi School of Medicine.

From the Department of Neurology, Columbia University College of Physicians and Surgeons.

1. Benda, C. E., and Cobb, S.: On the Pathogenesis of Paralysis Agitans (Parkinson's Disease), *Medicine* 21:95, 1942.

tion. There were changes also in the cerebral cortex, in the pons and in the region of the third ventricle.

In this case advanced pathologic alteration of the right substantia nigra was associated with tremor of the left side.

CASE 8 (Benda and Cobb¹).—*History and Examination*.—The patient had been a backward child, even with special tutoring. He was subject to convulsions during the last years of his life. In a typical attack, he would be found stretched out in bed with head and eyes turned to the right and frothing at the mouth. The right leg jerked spasmodically, and the left arm and leg were stiff. Then followed jerking of the right arm and twitching of the right side of the face. After the attack the tongue appeared to protrude to the left. The grasp of the left hand was weaker than that of the right. The arm reflexes were active and equal on the two sides.

A rhythmic tremor developed, involving especially the left arm and hand and the head, with cogwheel rigidity of the left arm and wrist. Death occurred at the age of 60. The diagnosis was hemiparkinsonism.

Microscopic Study.—Degeneration of cells was widespread in the pallidum, the caudate nucleus and the putamen. The substantia nigra showed patchy degeneration bilaterally, especially on the left side. The inferior olivary nuclei were gliotic. There was fatty degeneration in the nuclei of the tenth, eleventh and twelfth cranial nerves. An angioma was present in the right temporal lobe.

In this case the tremor and rigidity were on the same side of the body as was the more severely involved substantia nigra.

CASE 2 (McAlpin²).—*History and Examination*.—A man aged 43 had onset of symptoms in March 1924 with diplopia and insomnia, followed by lethargy. He remained in the hospital four months and during that time began to show signs of parkinsonism. Akinesia and generalized hypertonus were so extreme that he could not walk. There was no tremor. Death occurred on June 11, 1925.

Microscopic Study.—The only significant lesion was a pronounced alteration of the substantia nigra.

In this case the patient was reported to be without tremor, despite the pronounced alteration of the substantia nigra.

Cerebral Cortex.—The cerebral cortex may or may not be the seat of pathologic change.

CASE 4 (Liber and Neustaedter³).—*History and Examination*.—A woman aged 24 had the onset of her illness in 1925, characterized by unconsciousness without convulsions. There were generalized muscular pains. She was discharged as recovered in two weeks. Three months later there were tremor of the head and arms and difficulty in walking. She was readmitted to the hospital in May 1926.

Examination revealed tremor of the head and arms, general muscular weakness and slight muscular rigidity. The abdominal reflexes were absent; the plantar

2. McAlpine, D.: The Pathology of the Parkinsonian Syndrome Following Encephalitis Lethargica, with a Note on the Occurrence of Calcification in This Disease, *Brain* 46:255, 1923.

3. Liber, A. F., and Neustaedter, M.: Concerning the Pathology of Parkinsonism (Idiopathic, Arteriosclerotic, and Post-Encephalitic), *J. Nerv. & Ment. Dis.* 86:267, 1937.

response was normal, but the knee jerk was slightly exaggerated. The pupils were irregular but equal on the two sides; convergence was poor; the light reflex was fair; accommodation was good. A year after admission slight ankle clonus developed on both sides.

Death occurred in February 1934.

Microscopic Study.—Cerebral Cortex: The cortex was normal.

Striatum: The large cells showed disintegration, but the small cells were generally intact.

Globus Pallidus: The ganglion cells were unequal in size. Some appeared normal, but most were small and pyknotic. Many cells were fragmented.

Substantia Nigra: This structure was conspicuously altered. In some regions a few cells were intact.

Cerebellum: Many Purkinje cells were missing. Those present appeared normal. In the dentate and globose nuclei there were islands of atrophic cells.

Substantia Innominata of Reichert: Some cells showed pale cytoplasm. Most of the cells contained an abundance of yellow pigment.

Clastrum: Most of the cells were pyknotic but showed no other change.

Red Nucleus: The large cells revealed a moderate amount of destruction. The small and middle-sized cells had practically disappeared.

Medulla (two levels): This region was essentially normal except for the inferior olivary nucleus, the cells of which were pyknotic and shrunken.

Spinal Cord (first cervical segment): The structure was normal.

This case reveals the diffuse nature of the lesions in postencephalitic parkinsonism. The cortex was reported, however, as appearing within normal limits.

CASE 2 (Keschner and Sloane⁴).—*History and Examination.*—A woman aged 24 had a history of encephalitis about one year before her admission to the hospital, while pregnant. Several months after the attack she was unable to use the right upper and lower extremities. This condition was associated with grinding of the teeth and spasmodic contractions of the jaws. She also had severe headaches during this period.

Examination revealed a resting tremor of the right hand and of the head. Muscular rigidity was generalized but was severer on the right side than on the left. There were an extensor plantar response and patellar clonus bilaterally. Convergence was poor; the light reflex was weak, and accommodation was fair. Psychic disturbance revealed itself in lack of interest, untidiness and restlessness. The face was greasy, and saliva drooled from the mouth.

Microscopic Study.—The frontal lobes, thalamus, neostriatum, pons, medulla and cerebellum were normal in appearance. The pallidum, red nucleus and subthalamic nucleus showed only slight perivascular infiltration.

The substantia nigra showed diffuse swelling and destruction of its cells and a conspicuous increase in glia. No neuronophagia was seen. In some sections no remnants of pigment were evident, the cells appearing entirely washed out. The cresyl violet stain showed diminution in the number of cells of the locus caeruleus. Many cells were swollen and exhibited condensation of pigment.

4. Keschner, M., and Sloane, P.: Encephalitic, Idiopathic and Arteriosclerotic Parkinsonism, *Arch. Neurol. & Psychiat.* 25:1011 (May) 1931.

In this case there was little evident pathologic change, but much was left unexplained in the pathologic report. The substantia nigra reflected the greatest damage.

CASE (Weisenburg and Alpers⁵).—*History and Examination*.—A man aged 36 was admitted to the hospital in March and died in April 1925. The onset of illness occurred in November 1924. While at work he began to feel drowsy and continued so for about ten days, when he had to go to bed. Diplopia was also present. He slept all day but poorly at night. In January 1925 he began to have sharp pains in both hands, being severest in the knuckles. The hands became permanently clenched. In February the patient noticed stiffness in the right leg, which soon became completely stiffened. Soon afterward the left leg became stiff. The patient was also troubled with profuse perspiration and ptosis.

There was masking of facial expression, and perspiration was extreme. There was flexor contraction of the arms, hands and fingers. The legs were in rigid extension. The legs and arms could be placed in various positions, which were maintained. The right pupil was larger than the left, but all the cranial nerves were normal. The arm reflexes were barely noticeable because of the rigidity. The patellar and achilles tendon reflexes could be elicited. Neither clonus nor the Babinski sign was elicitable. Active movements were not possible. The Magnus and deKleijn reflexes were not tested.

Gross Pathologic Study.—The brain showed cortical atrophy, especially of the frontal lobes.

Microscopic Study.—The frontal cortex showed a slight disturbance in architecture, especially in the third layer. Satellitosis was evident in the various cortical layers and was widespread. In most of the cells the Nissl substance was absent.

The caudate nucleus for the most part was normal. There was, however, some involvement of the large cells. The small cells of the putamen were normal. Practically all its large cells showed degenerative changes. The cells of the globus pallidus showed slight involvement, but no reduction in number.

In the substantia nigra the cells of the medial group of the zona compacta were greatly reduced and the remainder swollen. Perivascular infiltration was present.

In the red nucleus the pars magnocellularis showed definite cellular changes, varying from satellitosis to complete neuronophagia. The pars parvocellularis showed even severer alterations. The subthalamic nucleus showed no deviation from normal. The medulla was reported as normal, as was the spinal cord.

The authors observed that this case presented a picture considerably like that of the "decerebrate" state. One of the preceding cases (case 4 of Liber and Neustaedter³), although unlike Weisenburg and Alpers' case in its clinical aspects, also showed destruction of the red nucleus.

Globus Pallidus.—The pallidum may or may not be the seat of extensive pathologic change.

CASE 3 (Keschner and Sloane⁴).—*History*.—A woman aged 36 was admitted to the hospital in December 1922 and died in June 1927. She had had influenza (?) in 1919. About one year later tremor, bradykinesia and slowness of speech developed.

5. Weisenburg, T. H., and Alpers, B. J.: Decerebrate Rigidity Following Encephalitis, Arch. Neurol. & Psychiat. 18:1 (July) 1927.

Examination revealed cogwheel rigidity of all four limbs and a parkinsonian tremor. The plantar responses were normal, but Hoffmann's sign was elicited bilaterally. The abdominal reflexes were active. In July 1923 the rigidity became so severe that she appeared to be in a partial "decerebrate" state. The head was in extreme hyperextension. The pupils reacted poorly to light but reasonably well in accommodation. The patient had attempted suicide before coming to the hospital.

Microscopic Study.—The meninges, cerebral cortex, cornu ammonis, external geniculate bodies, anterior corpora quadrigemina, pons, medulla, hypothalamus, corpus Luysii, cerebellum and red nuclei all appeared normal.

The lateral nucleus of the thalamus showed perivascular infiltration. Both the large and the small cells of the pallidum were darkly stained. The nuclei of the small cells were unusually large. The large cells showed moderately early degenerative changes. A slight increase in glia, without neuronophagia, was present. The putamen was similar to the pallidum. There was no evidence of perivascular infiltration in the striatum.

The caudal portion of the substantia nigra showed great diminution in the number of cells, the remaining cells being swollen and severely degenerated. The glial tissue was greatly increased.

The locus caeruleus was similar to the substantia nigra.

The globus pallidus showed slight état criblé.

The principal lesion in this case was, accordingly, located in the lentiform nucleus and the substantia nigra.

CASE (Holman⁶).—History.—A man aged 36, on March 12, 1920, became dizzy, had low grade fever, experienced pain in the elbow and was overtalkative and euphoric. A week later he became cyanotic, listless and seclusive. On March 20 he had generalized tremor, and became restless and sleepless. On March 29, his speech became thick, there was difficulty in swallowing and diplopia developed.

Examination revealed that the reflexes were hyperactive but equal on the two sides; there were a coarse tremor of the extremities and masklike facies. General weakness was present, and he held positions as though cataleptic. His temperature at the time of examination was 100.6 F., and the white blood cell count was 12,600.

There was a progressive increase in rigidity. The temperature continued to range from 99 to 103 F. as long as the patient lived. In the latter part of the illness the deep reflexes were more active on the left side than on the right. Death occurred on June 17, 1921.

Microscopic Study.—**Right Putamen and Caudate Nucleus:** The number of small and large cells was not diminished. Many of the large cells were practically normal, but some showed severe alteration. The small cells presented a similar picture.

Right Globus Pallidus: The large cells were normal in number and in a much better state of preservation than those in the putamen and the caudate nucleus of that side.

Left Putamen: The large cells were reduced in number but were better preserved than those on the right side. The small cells were also better preserved than those on the right.

Left Globus Pallidus: The cells were normal.

6. Holman, L. B.: The Histopathology of Post-Encephalitic Parkinson's Syndrome, Bull. Johns Hopkins Hosp. 36:403, 1925.

Substantia Nigra (left and right): Whole islands of pigment cells were wiped out. The remaining pigment cells were degenerating.

Subthalamic Body: The structures were normal.

Inferior Olivary Body: The cells were intact.

Nucleus Ambiguus: Alterations were present but were not greater than were to be expected from the fever.

Reticular Substance: The large motor cells were altered.

Dorsal Vagal Nucleus: The cells were affected.

Spinal Cord: The anterior horn cells showed changes attributed to the febrile state.

Precentral Cortex (left): There was damage to the larger pyramidal cells.

The diffuse nature of the lesions associated with postencephalitic parkinsonism is evident in this case, but most of the pathologic alteration was located in the striatum. The precentral cortex was also injured.

Cases such as the preceding ones offer many difficulties to acceptance of the belief that parkinsonism is based on a simple, specific neuropathologic process. It is, perhaps, in Hunt's⁷ syndrome of juvenile paralysis agitans that the concept of such specificity reached its highest development. This syndrome usually begins before adolescence and is slowly progressive. As far as could be ascertained, Hunt published only 1 autopsy report. This revealed a selective destruction of the large cells of the lenticular nucleus. A corroborative autopsy was reported by van Bogaert.⁸

One of the difficulties attendant on any attempt to determine just what neuropathologic factors are responsible for parkinsonism is the possibility not only that the disease may require multiple lesions but also that certain lesions of the neuroaxis may prevent its appearance in typical form. Recent neurosurgical experience has suggested that parkinsonism may be abolished or so altered as to be unrecognizable after operation on the frontal lobe. Such cases have appeared in the older literature from time to time.

Garcin and associates⁹ gave the following account of a case of left-sided parkinsonian syndrome. The patient, a man aged 45, showed rigidity of the left side with cogwheel phenomena and absence of associated movements on that side and masking of facial expression. The "postural reflexes" were hyperactive. No other abnormal reflexes were found. A very fine tremor of both upper limbs was present. The patient had been subject to intermittent seizures for a number of years; papilledema developed a short while before operation. At oper-

7. Hunt, R.: Progressive Atrophy of the Globus Pallidus, *Brain* **40**:58, 1917.

8. van Bogaert, L. M.: Contribution clinique et anatomique à l'étude de la paralysie agitante, juvénile primitive (Atrophie progressive du globe pâle de Ramsay Hunt), *Rev. neurol.* **2**:315, 1930.

9. Garcin, R.; Klein, M. R.; Kipper, M., and Le Bozec: Hémisindrome parkinsonien gauche par tumeur fronto-calleuse droite disparaissant complètement après ablation de celle-ci (présentation de malade), *Rev. neurol.* **75**:80, 1943.

Author	Case No.	Cerebral Cortex	Cerebellar Cortex	Dentate Nucleus	Ansa Lenticularis	Inferior Olivary Nucleus	Pallidum	Striatum	
								Small Cells	Large Cells
Barretto Netto, M.: Arch. brasil. de med. 34:107, 1944	2	+	++	..	+++	..	++
Liber and Neustaedter ³	1	—	+	+	..	++++	+++	±	++
	2	—	+	++++	..	++++	+++	±	++
	3	—	+	+	..	++++	+++	±	++
	4	—	+	++	..	++++	+++	±	++
	5	—	+	+	..	++++	+++	±	++
	7	—	+	+	..	++++	+++	±	++
	8	—	+	+	..	+	+++	±	++
	9	—	+	+	..	++++	+++	±	++
	10	—	+	+	..	++++	+++	±	++
	11	—	+	+	..	++++	+++	±	++
Hunt, J. R.: Arch. Int. Med. 22:647 (Nov.) 1918...	1	—	—	—	+	—	±	—	++
Keschner and Sloane ⁴	2 §	—	—	—	++	—	++	—	+++
	1	±	—	—	—	—	±	++	++
	2	—	—	—	—	—	±	—	—
	3	—	—	—	—	—	++	+	++
	4	—	—	—	+	—	++	+	++
	5	†	+	++	—
	6	—	—	—	—	..	+	±	++
Benda and Cobb ¹	7	†	++	+	+
	1	++	+++	±	+	+
	2	++	+	++	++	..	++	+	+
	3	++	++	±	±
	4	+++	++	..	++	+	+
	5	++	..	++	+++	++	++
	6	++	++	—	++	+++	+++
	7	++	+	+	+	++	++
	8	+	++	+	++	++	++
Hohman ⁶	+	±	+	+
Hunt ⁷	—	—	—	+	—	+++	—	—
McKinley, J. C.: Arch. Neurol. & Psychiat. 9:47 (Jan.) 1923	..	—	—	—	+	—	±	±	±
McAlpine ²	1 (1923)	—	—	±	±	+	+
	2 (1923)	—	—	—	..	—
McAlpine, D.: Brain 49:524, 1926.....	1 (1926)	—	—	—	—	—	..	—	—
	2 (1926)	—	—	—	—	..	Focal lesion	†	†
	3 (1926)	—	—	—	..	—	+	—	—
	4 (1926)	—	—	—	..	—	+	—	—
	5 (1926)	—	—	—	..	—	±	—	—
	6 (1926)	—	—	—	—	—	—
	7 (1926)	—	—	—	±	±	±
	8 (1926)	—	—	—	—
Bahr, M. A.: J. Nerv. & Ment. Dis. 82:514, 1935...	1	++	..	+++	+	—	+	±	±
	2	+	..	—	+	—	+	+	+
Weisenburg and Alpers ⁵	1	++	—	+	—	++
Davison, C.: A. Researh. Nerv. & Ment. Dis., Proc. 21:267, 1942	1	+	—	±	+	—	++	..	++
	2	—	—	—	++	—	+++	..	+
	3	±	—	+	+	—	++	..	++
	4	—	..	—	+	—	++	+	—
	5	—	..	—	+	—	++	—	—
	6	++	+	+	+	—	++	++	++
	8	—	—	—	±	—	—
	10	±	+	—	++	++	++
	11	+	+++	++	+	+

* In this table, — indicates absence of lesions; ±, questionable structural change; +, slight alteration; ++, moderate change; +++, severe alteration, and +++++, almost total destruction.

The symbols + and — were chosen because they reveal at a glance the relative involvement of different areas. They do not necessarily represent the evaluations of the original worker unless similar symbols were employed. All spaces were filled in as completely as the literature allowed.

*Parkinsonism Reported in the Literature**

[illegible]

† Only midbrain and basal ganglia studied.

§ Juvenile paralysis agitans.

ation, performed after ventriculographic study, a tumor about the size of an orange was removed from the right frontal lobe. The posterior portion of the tumor was slightly anterior to the motor cortex. It extended through the corpus callosum to the opposite side. The tumor filled the frontal horn of the right lateral ventricle. It infiltrated the caudate nucleus and probably the anterior part of the thalamus. After the operation the parkinsonian syndrome cleared completely. Histologically, the tumor was an astroblastoma.

Another condition which has some of the attributes of the parkinsonian syndrome, but which as yet has received no nosologic position, is that described by Hallervorden and Spatz¹⁰ and other neuropathologists. The condition is characterized by progressive muscular rigidity, affecting several members of the same family and occasionally associated with a rhythmic tremor or athetosis. The pathoanatomic change is said to consist in striking pigmentation of the globus pallidus and substantia nigra, the iron-containing pigment being seen in neurons and glial cells and lying free in the tissues. The neurons of the pigmented fields show degenerative changes. However, Helfand¹¹ stated that in his case there was reduced pigmentation of the zona compacta of the substantia nigra, as well as reduced iron content of the dentate nucleus.

One's understanding of the neuropathology of paralysis agitans is not increased by the presence of some unusual cases in the literature. One such case was reported by Keschner and Sloane. A man aged 53 exhibited a parkinsonian picture, including masklike facies, loss of normal associated movements, flexion of the head, cogwheel phenomena of the left upper extremity, monotonous speech and fine tremor of the head and hands. In addition, there were signs referable to the pyramidal tract in both lower extremities and some ataxia of the left arm. The patient died of agranulocytosis eight months after admission to the hospital. Histologic examination revealed no pathologic changes anywhere in the brain except in the inferior olives. Guillain and associates¹² reported a similar case.

The degree and nature of existing discrepancies are sufficiently apparent from the foregoing presentation to indicate the fruitlessness of a detailed description of all the available material. We have, therefore, prepared a tabulation of the location and degree of the pathologic alteration in the cases reported in the literature.

10. Hallervorden, J., and Spatz, H.: *Eigenartige Erkrankung im extrapyramidalen System mit besonderer Beteiligung des Globus pallidus und der Substantia nigra*, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **79**:254, 1922.

11. Helfand, M.: *Status Pignientatus*, *J. Nerv. & Ment. Dis.* **31**:662, 1935.

12. Guillain, G.; Mathieu, P., and Bertrand, I.: *La rigidité d'origine olivaire*, *Ann. de méd.* **25**:460, 1929.

In the 53 cases presented as pathologic studies of parkinsonism there is no unanimity of opinion as to the location of the structural change. However, moderate alterations (2 plus or more) were reported to have been exhibited in the substantia nigra in 44 of the 52 cases in which this structure was available for study, in the pallidum in only 29 of the 51 cases in which it could be studied and in the striatum in only 27 of the 51 cases in which it was available.

Since it is known that the substantia nigra undergoes degeneration when the corpus striatum is injured, it is of importance, in coming to a decision as to whether its pathologic condition is primary or secondary, to observe whether this structure was affected in any cases in which lesions were not exhibited in the corpus striatum. Examination reveals that the corpus striatum was not affected in 2 cases in which pathologic changes occurred in the substantia nigra. In 3 cases there was but doubtful involvement of the corpus striatum, and in 7 cases the pathologic alteration in the latter structure was slight. Approximately 10 per cent of the cases, therefore, suggest that the pathologic process in the substantia nigra is of a primary type. On the other hand, in all 5 cases in which the substantia nigra was reported normal and in the 1 case in which the pathologic alteration was doubtful definite lesions were exhibited in the corpus striatum. This suggests a probable error in the material of over 11 per cent, indicating that it would be unsafe to come to any conclusion as to whether the nigral pathologic process is of primary or secondary nature.

A disquieting feature of the evidence disclosed by the table is the disagreement between the strong internal consistency of the pathologic changes reported by certain authors and the inconsistency when these observations are compared with the pathologic picture reported by others. This has already been discussed. Thus, in all the cases reported by Benda and Cobb alterations were present in the cerebral cortex. In none of Neustaedter's or McAlpine's cases were such lesions present. Nearly all of the cases with a normal substantia nigra were reported by Hunt. In all of Neustaedter's cases, but in only 1 of Hunt's, were there lesions in the cerebellar cortex, the dentate nucleus, the inferior olive and the red nucleus. It is clear that differences of criteria or technic must be responsible for such a situation.

Despite the existence of a number of unusual cases in the literature, in the majority of cases of the parkinsonian state the greater share of the lesions are within the corpus striatum and the substantia nigra. Associated with this picture are minimal diffuse alterations. However, there are sporadic cases in which great destruction appears in almost any suprasegmental nucleus.

A possible explanation of the variations in lesions encountered in studies of the pathology in parkinsonism would be to assume that park-

insonism is not a distinct clinicopathologic state but merely an accumulation of superficially similar clinical disorders. At least three clinical varieties of parkinsonism have been distinguished: the idiopathic, the postencephalitic and Hunt's juvenile type, or what may be called heredoparkinsonism. As has already been noted, the pathologic process of the third form was regarded by Hunt to be essentially similar to that present in other forms of the disease. Whether or not there exists a differential pathologic picture for idiopathic paralysis agitans and postencephalitic parkinsonism is as yet unsettled.

Another unsettled problem is the condition of the precentral motor cortex in parkinsonism. There is great need for a thorough clinicopathologic investigation, not merely of this area but of the entire neuraxis, by modern methods of study and according to consistent criteria, applied over a large series of recent cases with autopsy.

It is difficult to tabulate the material of many of the foreign authors. In order that this material may not be neglected, it is necessary to discuss it briefly. Many of these authors (Spatz, in his preface to Klaue's¹³ paper; Klaue,¹³ Hassler¹⁴ and Trétiakoff¹⁵) expressed the belief that lesions of the substantia nigra are the most constant and the severest of any associated either with paralysis agitans or with postencephalitic parkinsonism and, moreover, that they are specific for these two diseases. Trétiakoff was among the first to emphasize the apparent constancy of such lesions in paralysis agitans. On the other hand, he not only gave a brief description of eleven other diseases in which alterations of the substantia nigra were noted but also observed that he had never seen a case in which the substantia nigra only was involved. His cases are not reported here, since his interest was limited to the pathology of the substantia nigra and the surrounding midbrain.

Emma¹⁶ studied the substantia nigra in 65 cases with varied causes and without extrapyramidal signs. In 21 of this series, alterations were present in the substantia nigra. The conclusion was reached, accordingly, that such lesions were reactions to nonspecific morbid stimuli.

Klaue based his conclusions on a study of the brains in 32 cases of paralysis agitans and 28 cases of postencephalitic parkinsonism. As controls, he studied the brains of 12 persons who had shown no neurologic or psychic disease and who had died between the ages of 51 and

13. Klaue, R.: Parkinsonsche Krankheit (Paralysis agitans) und postencephalitischer Parkinsonismus, *Arch. f. Psychiat.* **111**:251, 1940.

14. Hassler, R.: Zur Pathologie der Paralysis agitans und des post-enzephalitischen Parkinsonismus, *J. f. Psychol. u. Neurol.* **48**:387, 1937.

15. Trétiakoff, C.: Contribution à l'étude de l'anatomo-pathologie du locus niger de Soemmering, Thesis, Paris, no. 293, 1919.

16. Emma, M.: Contributo alla conoscenza della istopatologia della substantia nigra, *Riv. di pat. nerv.* **36**:483, 1930.

83 years. After this, he examined 10 brains of persons with senile dementia or schizophrenia who had exhibited no clinical signs of extrapyramidal disease.

He reported that, of his controls, some showed that a decrease in bulk of the frontal lobes was due to a disappearance of cortical cells accompanied with some increase in glial elements. The striatum was practically free of disease. Some of the brains had pallidal lesions, which consisted of accumulations of lipid pigment and consequent pigment atrophy, with some disappearance of nerve cells. Glial alterations were also observed. The vessels of the pallidum showed pseudocalcification, of varying intensity. Even very old patients could, however, be free of these changes. The substantia nigra was always normal.

Klaue said that his observations were in complete agreement with those of Gellerstedt¹⁷ in 50 normal cases of old people and by Oseki¹⁸ in 10 cases, adding that the last author stressed the fact that the lesions observed in the basal ganglia of normal aged persons were not less pronounced than those described by Lewy¹⁹ in patients with paralysis agitans.

Klaue gave a complete pathologic report of only 2 cases, which he considered illustrative of the typical pathologic pictures of the two types of disease, paralysis agitans and postencephalitic parkinsonism. His opinion on the pathology of paralysis agitans may be summarized as follows:

In the substantia nigra, all cell groups of the black zone of the zona compacta showed pathologic alterations with complete disappearance of some cell islands. Such changes were more striking in the caudal region of this nucleus. The locus caeruleus showed changes similar to those in the substantia nigra, but of milder degree. Pigmentary atrophy was observed in the inferior olives. The cerebral cortex, basal ganglia, dentate nucleus and cerebellar cortex were all within normal limits.

This picture may be contrasted with the pathologic substrate of postencephalitic parkinsonism as he described it. In this disease, the lesions of the substantia nigra were concentrated in the zona compacta but were more diffuse and complete than in paralysis agitans. The cerebral cortex and basal ganglia were not involved. No definite lesions were noted in the nuclei of the hypothalamus; but the locus caeruleus, again, was observed to be altered like the substantia nigra, but to a milder degree than the zona compacta.

17. Gellerstedt, N.: Zur Kenntnis der Hirnveränderungen bei der normalen alters-involution. *Upsala läkaref. förh.* 38:193, 1933.

18. Oseki, M.: Ueber die Veränderungen des Striatum im normalen Senium, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* 26:339, 1924.

19. Lewy, F. H.: Zur pathologischen Anatomie der Paralysis agitans, *Deutsche Ztschr. f. Nervenhe.* 50:50, 1913.

Klaue expressed the belief that the pathologic changes of paralysis agitans were not fundamentally different from those of postencephalitic parkinsonism and argued that this supported his belief that two diseases have the same etiologic agent. He was convinced that the lesions of the substantia nigra form the pathologic substrate of both paralysis agitans and postencephalitic parkinsonism. In his foreword to Klaue's paper, Spatz concurred in these views.

In an elaborate study of the organization of the substantia nigra, Hassler¹⁴ said that a somatotopical arrangement of the cell groups of the zona compacta is probable; that is, according to his cytoarchitectural designations, areas Spvl and Spev would appear to be related to the function of the arm. He explained the supposed specificity of the lesions in paralysis agitans and postencephalitic parkinsonism by postulating special pathoclitic properties of the cells of the zona compacta for a noxious agent common to the two conditions. Such pathoclitosis, he stated, also existed to a less extent in the cells of the locus caeruleus and the dorsal vagal nucleus.

When one remembers the disproportionality in pathologic methods for demonstrating alterations in large cells as against small cells and in large fibers as compared with small fibers, together with the difficulty in controlling the condition of the autopsy material, one can appreciate the task which confronts the pathologist. If one adds to this the little understood effects of lesions on ascending and descending tracts and nuclei (Hare and Hinsey,²⁰ Tower,²¹ Lassek,²² Hunt²³ and Davison,²⁴) it would not be surprising to find that classic pathology may fail to account for all the morbid processes in the diseases discussed.

CONCLUSIONS

No constant pathologic substrate for parkinsonism may be determined from the cases reported in the literature. The possibility that parkinsonian states are a complex rather than a single clinicopathologic entity might explain such a situation, but the common clinical elements seen among all such cases should be reflected in a common pathologic factor. The most common alteration is that in the substantia nigra, and the most consistent clinical finding is the peculiar tremor. The fact

20. Hare, W. K., and Hinsey, J. C.: Reactions of Dorsal Ganglion Cells to Section of Peripheral and Central Processes, *J. Comp. Neurol.* **73**:489, 1940.

21. Tower, S. S.: Pyramidal Lesion in the Monkey, *Brain* **63**:36, 1940.

22. Lassek, A. M.: The Pyramidal Tract (A Study of Retrograde Degeneration in the Monkey), *Arch. Neurol. & Psychiat.* **48**:561 (Oct.) 1942.

23. Hunt, J. R.: Retrograde Atrophy of Pyramidal Tract, *J. Nerv. & Ment. Dis.* **31**:504, 1904.

24. Davison, C.: Syndrome of Anterior Spinal Artery of the Medulla, *Arch. Neurol. & Psychiat.* **37**:91 (Jan.) 1937.

that the substantia nigra is not invariably involved in cases of such tremor not only may represent errors in interpretation but may suggest that the critical focus is in the vicinity of the substantia nigra rather than in this structure itself. The fact that tremor may not exist with lesions in the substantia nigra need not imply that such changes are without significance, since lesions situated elsewhere in the neuraxis may prevent or mask the appearance of such tremor.

Since parkinsonian states so frequently involve multiple lesions, it would be unwise to discard the possibility that more than one lesion is required for their maturation. Certainly, the multiple lesions which commonly exist do alter the clinical aspects of the case. What may be the minimal accessory pathologic changes required to produce the clinical picture one has no means of knowing, since really comprehensive studies on statistically significant, uniformly fresh material have still to be made.

Department of Neurology, Columbia University College of Physicians and Surgeons.

Case Reports

BENIGN FOCAL AMYOTROPHY

RICHARD B. DROOZ, M.D.*
HUNTINGTON STATION, N. Y.

OF THE great variety of neurologic disorders associated with atrophy of muscle, most fit into well delineated clinical and pathologic syndromes; yet the problem of the etiologic factors in the degeneration of muscle are among the least understood in neurology. Many generalized diseases may produce sharply localized areas of muscular atrophy, raising the question of why one group of muscles should be singled out to become atrophic while an analogous group is spared by a process acting equally on the two. For example, in hyperthyroidism, in which increased or altered thyroid hormone circulates through the entire body, all the muscles of the body may weaken, and perhaps waste somewhat; but in certain cases the tiny extraocular muscles may show degenerative changes far beyond those seen in other muscles. Lead and other metallic poisons, various hydrocarbons, diphtheria toxin and the poliomyelitis virus are but a few of the pathogenic agents which are distributed throughout the body of the host, yet may produce sharply localized disease of a neuromuscular unit. In reviewing the more important theories of the "enigma of myopathic predilection" in the muscular dystrophies, Wilson¹ stated: "It may be that the morbid processes depend on the constitution of individual muscles." There appears to be little reason to doubt that in neurology, as in other fields of medicine, the so-called selectivity of the site of action of a pathogenic agent may in large part be explained by locally diminished resistance to the onslaught of a noxious agent.

In 1902 Gowers,² lecturing at the National Hospital for the Paralyzed and Epileptic, urged acceptance of the concept of "muscular abiotrophy," postulating that individual muscles degenerate in the course of a diffusely acting pathogenic process because of an inherent predisposition of these muscles to destruction. Thus, whether a localized area of atrophy of muscle results from infection, endocrinopathy or defective metabolism, the specific site of the atrophy might depend on some local weakness or predisposition to atrophy in the presence of the diffusely acting pathogenic agent. Though this concept of "muscular abiotrophy" is a vague and unsatisfactory substitution of philosophy for factual knowledge, no better explanation has been given since.

This principle of greater susceptibility of individual muscles to degeneration is clearly demonstrated in certain lesions of the peripheral nerves. For example, Pollock,³ working with cases from World War I,

From Regional Station Hospital No. 2, Fort Bragg, N. C.

* Formerly Captain, Medical Corps, Army of the United States.

1. Wilson, S. A. K.: *Neurology*, London, Edward Arnold & Co., 1940, p. 989.

2. Gowers, W. R.: A Lecture on Myopathy and a Distal Form, *Brit. M. J.* 2:89-92, 1902.

3. Pollock, L. J.: Motor Disturbances in Peripheral Nerve Lesions: (A) Muscles Involved in Partial Lesions, (B) Order of Restored Motion, *Arch. Neurol. & Psychiat.* 14:675-684 (Nov.) 1925.

showed that "whether the nerve [is] slightly or severely injured, the muscles most frequently involved in ulnar nerve lesions are the same. The hypothenar group of muscles and the interossei were most frequently affected." Attempts have been made to explain these differences in susceptibility to degeneration in terms of distance from the nerve cell body, relative phylogenetic age of the muscles and various other factors; but, regardless of the exact mechanism, the fact remains that although the entire nerve has been injured, resulting in defective trophic influences on all muscles within the distribution of the nerve, certain of these muscles show a greater tendency to degenerate.

In terms of the concept of a muscle yielding to atrophy because of an inherent susceptibility, a patient studied at an Army general hospital offered an interesting problem for speculation. There rapidly developed, without known cause, atrophy sharply and exclusively limited to the muscles contained in the first interosseous space of the left hand. I believe no similar case has been reported.

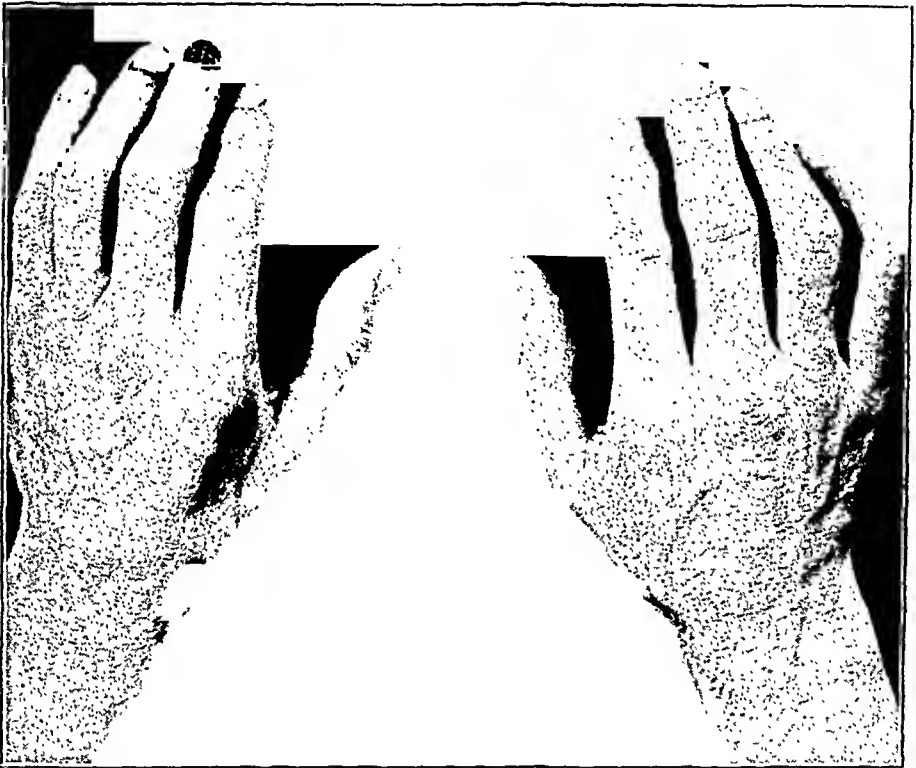
REPORT OF A CASE

History.—A white man aged 29, single, an infantry instructor sergeant who had spent his entire four and one-half years of military service within the continental United States, was admitted to an Army general hospital in December 1945 because of sharply localized atrophy of the small muscles between the thumb and the index finger of the left hand. He had been in excellent health until early in August 1945, when there developed acute nasopharyngitis, with increase in temperature up to 102 F. for a few days, mild malaise, mild diffuse aches and pains and small accumulations of mucus in the pharynx. The review of systems otherwise revealed nothing abnormal; specifically, he had no headaches, nausea, vomiting, stiffness of the neck or back or photophobia. He was hospitalized for nine days, not because he was excessively ill, but in line with Army policy in the control of diseases of the respiratory tract. He was then returned to duty with the diagnosis of "nasopharyngitis, catarrhal, acute, moderate." There appeared to be nothing unusual in the course of this nasopharyngitis. The record of his physical examination at that time stated specifically that his extremities were normal. While the hands might not be carefully inspected in the physical examination of a patient with nasopharyngitis, it is reasonable to believe that if at the time the atrophy in the accompanying photograph (figure) had been present it would not have escaped the attention of the medical officers, nurses and enlisted attendants, not to mention his own attention or that of the soldiers with whom he lived.

Within the few days or few weeks after his discharge from the hospital, he noted that the stability of the left index finger was poor and that the finger slipped when he attempted to use it. This was especially noticeable when he was handling table silver. At the same time, over the course of a few weeks, he noted rapidly progressive wasting of the muscles between the thumb and the index finger of the left hand. At the end of a few weeks there seemed to be no muscle substance remaining in the first interosseous space of that hand. When fasciculations were described to him and shown him in another patient, he expressed certainty that he had never had them in the area of muscular atrophy or elsewhere, and he seemed of a sufficiently observant nature to be reliable on this point.

Shortly after progression of the atrophic process ceased, he became eligible for discharge from the Army because of his adjusted service rating ("discharge

points"). He was, however, persuaded to permit study in the hospital prior to separation. On Dec. 1, 1945 he entered an Army regional hospital, where he was studied for one month. While in that hospital, he participated extensively in reconditioning exercise of his hand, through which he believed he had regained almost normal strength of the left index finger and thumb. He stated that the amount of atrophy had remained unchanged since about October 1945, the atrophic process having run its complete course over a period of one or, at most, two months. On Dec. 30, 1945 he came under my observation, when he was transferred to an Army general hospital with the diagnosis of "other diseases⁴ of the nervous system, manifested by weakness of the left index finger and atrophy of muscles between the thumb and the index finger on the dorsal surface of the left hand; cause undetermined."



Atrophy of muscles of the first interosseus space of the left hand.

The patient had had no exposure to heavy metals or to other chemicals. His use of alcohol was very moderate, and he had no abnormalities in his diet or "food fads." He had no history of allergic disorder. Review of the various systems and of his past medical history revealed that he had been healthy throughout life except for the benign illnesses of childhood and occasional colds in adult life. At no time in his life, either civilian or military, had he been employed at a job involving repeated or protracted trauma to the palm of his hand. He had never had a fracture of the elbow or elsewhere in the vicinity of the ulnar nerve. His family history revealed no neuropathic trait.

4. "Other diseases" refers to diseases not listed in any authorized military or civilian medical nomenclature.

Physical and Neurologic Examination.—The patient was well developed, husky and apparently in excellent general physical condition. The only physical abnormality noted was extreme atrophy of the small muscles between the thumb and the index finger of the left hand, involving the first dorsal interosseous muscle and the adductor pollicis. The atrophy of these muscles was sufficient to make the involved area sink in conspicuously (figure). The overlying skin showed no abnormality. There were surprisingly slight weakness of abduction of the left index finger and questionable minimal weakness of adduction of the left thumb. The *signe de journal* was only slightly positive, as evidenced by slight weakness of retention of a piece of paper between the thumb and index finger of the left hand as compared with that of the uninvolved (right) hand when the examiner pulled the piece of paper away. There was no atrophy of muscle elsewhere in the hand or in any other part of the body, and no fasciculations were noted on repeated examination. The rest of the neurologic examination, including specific functional tests of ulnar nerve, revealed no abnormality. The patient was right handed.

Laboratory Data.—Urinalysis and complete blood count gave normal results. The Kahn reaction of the blood was negative. Examination of the stool showed no ova or parasites. Roentgenographic study of the cervical portion of the spine showed no cervical rib or other significant bony abnormality. Spinal puncture revealed a clear fluid, under an initial pressure of 130 mm. of water; examination of the fluid showed 3 lymphocytes per cubic millimeter, a negative Pandy reaction, and 35 mg. of total protein per hundred cubic centimeters. There was no evidence of block in manometric tests. Electrical reaction of degeneration was not present. Faradic and galvanic responses were reported as "the same in the two hands except for slightly less strength in response of the adductor pollicis, the first dorsal interosseous and the first flexor profundus digitorum muscles on galvanic stimulation."

COMMENT

The conspicuous, sharply limited atrophy seen in this case was out of all proportion to the resultant minimal weakness of the involved muscles. There were no fasciculations, no electrical reaction of degeneration, no sensory signs or symptoms, no lesion of the cervical portion of the spine and no abnormalities of the spinal fluid.⁵ Observation of the patient could be well controlled in the sense that he was hospitalized and under observation during his nasopharyngitis, as well as later, and was examined by a number of medical officers, who concurred in the physical and neurologic findings. I am fortunate in having been able to secure a follow-up study of the patient for one year, and I can report that there has been no progression in the atrophy described in this paper, nor have any new neurologic symptoms appeared.

The muscles involved in this case, those which lie in the first interosseous space, are supplied by the deep palmar branch of the ulnar nerve. The first dorsal interosseous muscle, which abducts the index finger radiad and flexes the index finger at the metacarpophalangeal joint, makes up the greatest bulk of muscle in the first interosseous space. The adductor pollicis and the medial head of the flexor pollicis brevis (homologue of the first volar interosseous muscle) constitute the remaining bulk of the musculature.

5. Unfortunately, the spinal fluid was not examined until about two months after the atrophy had ceased to progress.

The muscles contained in the first interosseous space waste early and severely in a host of disorders of nerve and spinal cord, including ulnar neuropathy, amyotrophic lateral sclerosis and Aran-Duchenne muscular atrophy, but none of these conditions causes the sharply delimited, severe atrophy seen in this case, with little impairment of function, absence of fibrillations, normal electrical reactions, rapid progression of the atrophy during a few weeks, and then complete cessation of the process. A review of the available literature has disclosed no similar case.

The rapidity of development and limitation of the atrophy suggested first a neuropathic process, perhaps inflammatory, perhaps traumatic, limited to the distal portion of the ulnar nerve, the deep palmar branch. In 1908 Ramsay Hunt⁶ described the syndrome of "occupation neuritis of the deep palmar branch of the ulnar nerve." He emphasized the absence of the usual sensory signs and symptoms of neuritis because the deep palmar branch lacks a sensory component. His criteria for this neuritis were, first, atrophic paralysis of all the intrinsic muscles of the hand innervated by the ulnar nerve; second, electrical reaction of degeneration, and, third, absence of objective sensory disturbance in the distribution of the ulnar nerve. He expressed the belief that the "neuritis" resulted from compression of the deep palmar branch as it passes between the small muscles of the hypothenar eminence, as a result of a continued (occupational) pressure on this region of the palm. Subsequently, a number of cases of this syndrome have been reported by Harris⁷ and others. No case of "neuritis" of the deep palmar branch of the ulnar nerve showed the sharply limited atrophy present in the case reported here. Moreover, the absence of an electrical reaction of degeneration in the presence of severe atrophy argues, though not incontrovertibly, against a neuritic origin in the present case.

Discrete lesions of constituents of the brachial plexus have caused limited amyotrophies. Without any attempt at a review of the literature, one may point to Wilson's⁸ description, in 1913, of atrophy sharply localized to the region of the opponens pollicis and abductor pollicis muscles in cases of cervical rib. Photographs in such cases may also be found in his textbook,⁹ as well as in the 1913 report.⁸ In 1908 Thompson¹⁰ described "familial atrophy of the hand muscles." Thompson's cases were of interest in that 7 members of a family of 64 persons (five generations) exhibited atrophy sharply localized to the outer (radial) half of the thenar eminence. Roentgenograms of their spines showed the presence of cervical rib, a familial characteristic. Thompson

6. Hunt, J. R.: Occupation Neuritis of the Deep Palmar Branch of the Ulnar Nerve, *J. Nerv. & Ment. Dis.* **35**:673-689, 1908.

7. Harris, W.: Occupational Pressure Neuritis of the Deep Palmar Branch of the Ulnar Nerve, *Brit. M. J.* **1**:98, 1929.

8. Wilson, S. A. K.: Some Points in the Symptomatology of Cervical Rib, with Especial Reference to Muscular Wasting, *Proc. Roy. Soc. Med.* **6**:133-141, 1913.

9. Wilson,¹ pp. 1406-1416.

10. Thompson, T.: Familial Atrophy of the Hand Muscles, *Brain* **31**:286-300, 1908.

argued that the cervical rib was not the cause of the atrophy; but, as previously mentioned, later workers have shown that cervical rib is capable of causing atrophy as sharply defined as that found in Thompson's cases. In terms of the present case, this is of interest in demonstrating, first, that a lesion of components of the brachial plexus may cause sharply defined atrophy in the hand and, second, that, although the compressed elements of the plexus must have innervated more than the abductor pollicis and opponens pollicis, these muscles were for some reason less able to withstand the process leading to atrophy. In the case reported here there was no cervical rib nor other apparent bony abnormality to account for compression of cervical rootlets or of components of the brachial plexus, but a less apparent lesion might conceivably have existed.

"Distant wasting of the first dorsal interosseous muscle" associated with diminution of epicritic sensibility over the ulnar border of the hand was described by Buzzard¹¹ as a late sequel of fracture of the external condyle of the humerus seven years previously (rudimentary cervical ribs were also present). Unfortunately, no picture was furnished, and the description did not clearly indicate whether the atrophy was entirely localized to the first dorsal interosseous muscle. The possibility of this "tardy paralysis of the ulnar nerve," first described by Panas in 1878, named by Ramsay Hunt in 1916 and elucidated by a number of investigators,¹² could be ruled out in my case by careful inquiry into the history and by absence of valgus deformity at the elbow.¹³

In 1939 Wartenberg,¹⁴ under the title of "Partial Thenar Atrophy," reported 7 cases with certain points of similarity to the present case. As described by Wartenberg, this consisted of "a peculiar and distinct picture that I have not observed in any other neurologic disease. The cardinal sign in all cases was a partial, sometimes sharply defined, atrophy along the radial, outer, side of the thenar eminence." There was no cervical rib or other bony abnormality. Although 5 of his 7 patients noted paresthesias, there were "no appreciable sensory changes in the hands, fingers or elsewhere." There were no fibrillations. After commenting on the difficulties of electrical examination of the small muscles, Wartenberg noted that in some cases the muscles affected seemed not to react at all, in some cases there was complete reaction of degeneration and in no case was a movement of opposition of the thumb elicited by electrical stimulation. His final comment is of great theoretic interest:

. . . I prefer not to speak of neuritis and wish to lay more stress on the fundamental importance of the inherent abiotrophy of the two muscles of the hand that

11. Buzzard, E. F.: Some Varieties of Traumatic and Toxic Ulnar Neuritis, *Lancet* **1**:317-319, 1922.

12. Shelden, W. D.: Tardy Paralysis of the Ulnar Nerve, *M. Clin. North America* **5**:499-509, 1921.

13. Miller, E. M.: Late Ulnar Nerve Palsy, *Surg., Gynec. & Obst.* **38**:37-46, 1924.

14. Wartenberg, R.: Partial Thenar Atrophy, *Arch. Neurol. & Psychiat.* **42**:373-394 (Sept.) 1939.

are involved. Though the partial thenar atrophy may be precipitated by external causes, this constitutional abiotrophy is the primary factor and by itself can produce a pathologic condition of the hands.

In the present case the atrophy was as sharply delimited as in Wartenberg's, but in a different site. In this case, as in Wartenberg's, there was "predominance of the atrophy over the paralysis, whereas in a neuritic disorder one would expect the opposite to occur." One wonders whether his cases, as well as mine, might be included in a concept of a limited area of congenitally inferior muscle, predisposed to degenerate spontaneously or by reason of increased susceptibility to a generally acting pathogenic influence, such as neuritis, compression of the nerve or trauma. The term "benign focal amyotrophy" is suggested as being descriptive, but noncommittal regarding site of atrophy or individual precipitating cause.

In 1940 Romano and Michael¹⁵ described 3 cases of partial thenar atrophy, explaining their first case by brachial neuritis, the second by direct trauma to the nerve and the third by the assumption of "involvement of selective fibers of the median nerve," although the exact cause was not apparent. These explanations are in no way contrary to the concept that the inherent weakness of the two muscles involved predisposed them to atrophy, while other muscles innervated by the median nerve were able to withstand the pathologic process.

The preservation of normal electrical reactions in the case reported here, contrary to what is found in cases of neuritis, is curiously similar to what is observed with progressive muscular dystrophy. As Wilson commented¹⁶ in cases of progressive muscular dystrophy "stimulation with either faradic or galvanic current will continue to excite myoplasm so long as sufficient is left to respond." It may be that in either condition an inherent defect of muscle predisposes to degeneration of the affected muscles without interfering with the neuromuscular relation. From a highly theoretic point of view one may speculate on the possibility that some of the focal amyotrophies are formes frustes of the progressive muscular dystrophies.

One may also speculate on the relation between the patient's nasopharyngitis in the present case and his subsequent atrophy of the interosseous muscle. There is the reasonable objection that every neurologic syndrome has been preceded by an incidental "cold." In this connection, Barnes's¹⁷ "toxic degeneration of the lower neurones simulating peripheral neuritis" is often cited, but the absence at that time of modern aids to diagnosis, including spinal puncture, and his lack of histologic material led to misinterpretations drawn from a variety of cases, which appear to have included instances of neuritis and infectious neuronitis.

15. Romano, J., and Michael, M.: Partial Thenar Atrophy, *Arch. Neurol. & Psychiat.* **44**:1224-1229 (Dec.) 1940.

16. Wilson,¹ p. 977.

17. Barnes, S.: Toxic Degeneration of the Lower Neurones Simulating Peripheral Neuritis, *Brain* **25**:479-500, 1902.

SUMMARY

A case with rapidly progressive atrophy sharply and entirely limited to the muscles contained in the first interosseous space is reported. During a period of observation of one year, there has been no progression of the atrophy, and no new neurologic signs or symptoms have appeared. It is believed that no similar case has been reported. Attention is called to certain similarities of this disorder to the syndrome described by Wartenberg under the title of partial thenar atrophy. The name "benign focal amyotrophy" is suggested as descriptive of such an atrophy, but as noncommittal regarding the site of atrophy or individual precipitating cause. The concept that focal atrophies may be explained by an inherent inability of certain muscles to withstand the noxious influence of a process which acts on many or all muscles, yet produces atrophy of only a few, is discussed.

Hillside Drive.

News and Comment

RESOLUTION ADOPTED BY THE GROUP FOR THE ADVANCEMENT OF PSYCHIATRY AT MINNEAPOLIS, JULY 2, 1947

Because of recent newspaper and magazine articles which claim that a conflict exists between psychiatry and religion, and because of the resulting confusion of and the harm done to patients and their families, the membership of the Group for the Advancement of Psychiatry, meeting in Minneapolis, believe it is highly desirable to make the following statement:

"For centuries, religion and medicine have been closely related. Psychiatry, as a branch of medicine, has been so closely related to religion that at times the two were almost inseparable. As science has developed, however, medicine and religion have assumed distinctive roles in society, but they continue to share the common aim of human betterment. This also holds true for that method of psychiatry known as psychoanalysis.

"We, as members of the Group for the Advancement of Psychiatry, believe in the dignity and the integrity of the individual. We believe that a major goal of treatment is the progressive attainment of social responsibility. We recognize as of crucial significance the influence of the home on the individual and the importance of ethical training in the home. We also recognize the important role religion can play in bringing about an improved emotional and moral state.

"The methods of psychiatry aim to help patients achieve health in their emotional lives so that they may live in harmony with society and with its standards. We believe that there is no conflict between psychiatry and religion. In the practice of his profession the competent psychiatrist will, therefore, always be guided by this belief."

FACT SHEET

The Group for the Advancement of Psychiatry was organized in May 1946 in Chicago by a number of members of the American Psychiatric Association in an effort to accelerate psychiatric progress by mutual study and discussion of outstanding problems, clarification of concepts and determination of psychiatric needs and concrete steps required to meet those needs. The group now has 126 members from the United States and Canada, all of whom are also members of the American Psychiatric Association. Dr. William C. Menninger, of Topeka, Kan., is its chairman, and Dr. Henry Brosin, of Chicago, its secretary. Activities of the group are financed in part by a grant from the Commonwealth Fund.

The first formal meeting of the group was held Nov. 4 to 6, 1946, in Rye, N. Y., where the main subject of study and discussion was the problem of psychiatry in medical education. The second formal meeting, held at Minneapolis, June 30 to July 2, 1947, was devoted principally to the subject of state psychiatric hospitals.

The Group for the Advancement of Psychiatry comprises fifteen committees, covering medical education, research, preventive psychiatry, therapy, public education, social work, cooperation with federal agencies, cooperation with lay groups, state hospitals, racial and social problems, clinical psychology, industrial psychiatry, forensic psychiatry, international relations and child psychiatry. More than twenty experts in other fields have been invited to serve as consultants.

From time to time, the Group for the Advancement of Psychiatry has adopted reports and resolutions on some of the subjects studied by its committees. A number of these reports will be published in the near future in several professional journals.

AWARD OF FEDERAL GRANTS FOR RESEARCH IN MENTAL HEALTH, UNITED STATES PUBLIC HEALTH SERVICE

Award of the first federal grants for research in mental health under the new National Mental Health Act has been announced by Dr. Thomas Parran, Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C.

The mental health program, authorized by Congress in 1946, received its first appropriations, totaling \$7,500,000, on July 8, 1947. In addition to paying the cost of mental health activities within the Public Health Service, this is to finance a threefold program of research on mental illness, development of local mental health facilities and training of mental health personnel.

Grants announced today go to institutions and individuals to support research projects in fields bearing on the problems of mental illness. The grants were recommended by the National Mental Health Advisory Council, a body of experts in the mental health field, and were approved by the Surgeon General.

Twenty-five research grants have been awarded to the following institutions and individuals:

- Indiana University, Bloomington, Ind.; director of project: Dr. W. N. Kellogg, professor of psychology
- University of Kansas, Lawrence, Kan.; director of project: Dr. Roger C. Barker, professor of genetic psychology
- Dr. Anne Roe, 23-03 44th Drive, Long Island City 1, N. Y.
- State University of Iowa, Iowa City, Iowa; director of project: Dr. J. S. Gottlieb, associate professor of psychiatry
- Northwestern University Medical School, Chicago; director of project: Dr. Jules H. Masserman, assistant professor, Nervous and Mental Disease
- Chicago Institute for Psychoanalysis, Chicago; directors of project: Dr. Franz Alexander, director of institute and Dr. Thomas M. French, associate director of institute (three projects)
- The Menninger Foundation, Topeka, Kan.; directors of project: Dr. Eunice M. Leitch, assistant psychiatrist, Menninger Clinic, and Dr. Sibylle K. Escalona, assistant director, Division of Psychology, Menninger Clinic
- The Menninger Foundation, Topeka, Kan.; directors of project: Dr. Margaret Brenman, director of division of psychology, Menninger Clinic, and Dr. Merton Gill, assistant director of department of research, Menninger Foundation
- Jefferson Medical College, Philadelphia; director of project: Dr. Francis M. Forster, assistant professor of neurology
- The James Jackson Putnam Children's Center, Roxbury, Mass.; directors of project: Dr. Marian C. Putnam and Mrs. Beata Rank
- Cornell University, Ithaca, N. Y.; directors of project: Dr. Howard S. Liddell, professor of psychology, and Dr. Clive M. McCay, professor of nutrition
- University of Pittsburgh, Pittsburgh; director of project: Dr. Wayne Dennis, professor of psychology, and head of department of psychology
- Dr. Leopold Bellak, associate in psychiatry, New York Medical College; assistant psychiatrist, Flower and Fifth Avenue Hospitals, New York
- Washington School of Psychiatry, Washington, D. C.; director of project: Dr. Alfred H. Stanton, research associate
- Marriage Council of Philadelphia, Philadelphia; directors of project: Mrs. Emily Hartshorne Mudd, director of marriage council; Dr. Malcolm G. Preston, research consultant, and Dr. William L. Peltz, psychiatric consultant
- New York State Psychiatric Institute, New York; director of project: Dr. Zygmunt A. Piotrowski, associate in psychiatry
- Caroline Zachry Institute of Human Development, Inc., New York; director of project: Dr. Lawrence K. Frank, director of Caroline Zachry Institute
- Michael Reese Hospital, Chicago 16; director of project: Dr. Samuel J. Beck, head of psychology laboratory (two projects)
- Michael Reese Hospital, Chicago; director of project: Dr. Roy R. Grinker, director, Institute for Psychosomatic and Psychiatric Research and Training
- Massachusetts General Hospital, Boston; directors of project: Dr. Allan M. Butler, chief of the children's medical service, and Dr. Stanley Cobb, chief of the psychiatric service
- The May Institute for Medical Research of the Jewish Hospital, Cincinnati; director of project: Dr. I. Arthur Mirsky, director, The May Institute for Medical Research; associate professor of Experimental Medicine in Medicine; associate professor of Experimental Medicine in Psychiatry (two projects)

GRADUATE FELLOWSHIP AWARDS IN HEALTH EDUCATION, UNITED STATES PUBLIC HEALTH SERVICE

Twenty-five men and women in fifteen states, the District of Columbia and Alaska have been offered graduate fellowships in health education, financed by the National Foundation for Infantile Paralysis, March of Dimes Funds, as

announced by Dr. Thomas Parran, Surgeon General, United States Public Health Service, Federal Security Agency.

In addition to nine months of academic study at an accredited school of public health, starting September 1947, each fellow will have three months of field training in a health department under supervision of a public health educator. Of the 21 persons who have accepted the award, 17 will receive the degree of Master of Public Health, and 4 will receive the degree of Master of Science in Public Health, after satisfactory classroom work and field training.

The award winners, 4 of whom are veterans, were chosen from more than 340 candidates who submitted applications to the Committee on Training of Public Health Personnel of the United States Public Health Service.

The membership of the Health Education Fellowship Awards Committee is as follows: Dr. C. L. Williams Sr., United States Public Health Service, chairman; Dr. Ben W. Miller, American Association for Health, Physical Education and Recreation; Dr. Frank Stafford, United States Office of Education, Federal Security Agency; Dr. A. L. Van Horn, Children's Bureau, Federal Security Agency; Dr. G. M. Wheatley, American Public Health Association, and Miss Catherine Worthingham, National Foundation for Infantile Paralysis.

This year's winners make a total of 83 persons since 1944 who have been granted fellowships from the National Foundation for Infantile Paralysis for graduate study in the field of health education.

Persons who have accepted fellowships for 1947-1948 and the universities they will attend are:

University of California: Fern R. Fehlmán, Mount Morrison, Colo.; Alston H. Haggerty, Berkeley, Calif.; Rita M. Flick, Lewistown, Pa.; Margaret M. Warner, Oconto, Wis.
Columbia University: Anna Obert, Downey, Ill.; Rhoda Woronoff, Washington, D. C.
University of Michigan: Alice Beardslee, Richmond, Va.; George V. Leadbetter, Juneau, Alaska; Howard J. Stroud, Grand Rapids, Mich.; Greta K. Yager, Liberty, N. Y.
University of Minnesota: Ann Switzer, Forest Glen Section, Washington, D. C.
University of North Carolina: Ruth L. Coile, Pinehurst, Ga.; Margaret M. Ervin, Florence, S. C.; Eva V. Higdon, West Asheville, N. C.; Maryrose Johnson, New York; William R. Manning, Logan, Utah.
North Carolina State College: Ida B. Gadsden, Savannah, Ga.; Thomas E. Roberson, Laurel, Miss.
Yale University: Marjory Buntyn, Savannah, Ga.; Lena M. DiCicco, West Roxbury, Mass.; Beatrice A. Hruska, Helena, Mont.

APPOINTMENTS TO NATIONAL ADVISORY MENTAL HEALTH COUNCIL

Dr. Alan Gregg, director, the medical sciences, Rockefeller Foundation, New York, and Dr. Karl M. Bowman, Langley Porter Clinic, San Francisco, have been appointed as members of the National Advisory Mental Health Council of the United States Public Health Service, succeeding Dr. Frank F. Tallman, commissioner of mental hygiene, department of public welfare, Columbus, Ohio, and Dr. George S. Stevenson, medical director, National Committee for Mental Hygiene, New York, whose terms expired.

Dr. Tallman and Dr. Stevenson were appointed as consultants in mental health to United States Public Health Service on July 1, on expiration of their terms on the National Advisory Mental Health Council.

ABSTRACTERS FOR FOREIGN JOURNALS WANTED

Abstracters for French, German and Italian neurologic journals are wanted. The only compensation provided is a subscription to the periodical to be abstracted and to the periodical for which the abstracts are prepared. Please communicate with Dr. Bernard J. Alpers, 111 North 49th Street, Philadelphia 39.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE IN VIVO INACTIVATION BY CYANIDE OF BRAIN CYTOCHROME OXIDASE AND ITS EFFECT ON GLYCOLYSIS AND ON THE HIGH ENERGY PHOSPHORUS COMPOUNDS IN BRAIN. H. G. ALBAUM, J. TEPPERMAN and O. BODANSKY, *J. Biol. Chem.* **164**:45, 1946.

The investigations of Keilin and of Stotz have shown that the cyanide ion combines in vitro with cytochrome oxidase and thereby interferes with the utilization of molecular oxygen by the tissue oxidation-reduction systems. It has also been demonstrated that the utilization of molecular oxygen is coupled with phosphorylation reactions, and Lipmann has emphasized the role of aerobic metabolism in the resynthesis of high energy phosphorus compounds. In the intact animal, the resynthesis of high energy phosphorus compounds is coupled with oxidative processes. The present experiments were undertaken, first, to determine whether brain tissue from cyanide-poisoned rats showed a diminution in cytochrome oxidase activity and, second, to study in some detail the distribution of glycogen, lactic acid and the phosphorylated intermediate compounds in such tissue, particularly with reference to the distribution pattern of high energy phosphorus compounds. Rats given intraperitoneal injections of 5 mg. of sodium cyanide per kilogram of body weight showed approximately a 50 per cent decrease in cytochrome oxidase activity in the brain. The brains of these cyanide-poisoned rats showed significant decreases in the concentrations of glycogen, phosphocreatine and adenosine triphosphate and significant increases in the concentrations of inorganic phosphate, lactic acid, hexose diphosphate, phosphoglycerate and phosphopyruvate. These results indicate that anoxia in tissue induced by inactivation of cytochrome oxidase results in a shift from aerobic to anaerobic metabolism and a depletion of high energy phosphorus compounds.

PAGE, Cleveland.

GENERALIZED ATONIA AND PROFOUND DYSREFLEXIA FOLLOWING TRANSECTION OF THE BRAIN STEM THROUGH THE CEPHALIC PONS. ALLEN D. KELLER, *J. Neurophysiol.* **8**:275 (Sept.) 1945.

By means of blunt traction, Keller transected the brain stem of dogs at various levels of the midbrain and pons. The dogs were studied by gross clinical inspection for several weeks after operation. An important feature of the operative technic was the maintained integrity of the cerebral circulation. Transections of the upper portion of the pons invariably produced generalized and enduring muscular atonia. Profound dysreflexia occurred after transection of the brain stem at any level of the pons or midbrain. Dysreflexia was more profound in transections of the upper part of the pons. The degree and distribution of the dysreflexia varied somewhat with the level of transection. Spontaneous extensor rigidity did not routinely follow transections of the midbrain, nor was there increased resistance to passive manipulation of muscles. The reflex standing stance was not exaggerated. In low midbrain preparations righting reflexes were impaired.

FORSTER, Philadelphia.

ELECTRICAL ACTIVITY OF THE THALAMUS AND BASAL GANGLIA IN DECORTICATE CATS. R. S. MORRISON and D. L. BASSETT, *J. Neurophysiol.* 8:309 (Jan.) 1945.

Morrison and Bassett studied the electrical activity of the thalamus and basal ganglia of cats following decortication. For as long as three days typical bursts of 8 to 12 per second spikes were recorded. In 1 animal bilateral decortication, transection of the midbrain and section of both optic nerves failed to prevent the appearance of the bursts. In cats which had been decorticate from twenty-one days to one year, normal bursts did not appear, but bursts of atypical, low voltage activity occurred in restricted areas. Morrison and Bassett conclude that the spiking activity recorded from the thalamus does not depend in a functional sense on the presence of the neocortex, since they occur in the absence of a high proportion of normal thalamopetal impulses. The ultimate reduction in spiking activity recorded from the thalamus of decorticate preparations is probably due to the disintegration of elements of the thalamus dependent on the cortex for their anatomic integrity.

FORSTER, Philadelphia.

THE ELECTRICAL ACTIVITY OF VOLUNTARY MUSCLE IN MAN UNDER NORMAL AND PATHOLOGICAL CONDITIONS. G. WEDDLE, B. FEINSTEIN and R. E. PATTLE, *Brain* 67:178, 1944.

Weddle, Feinstein and Pattle obtained electromyographic records from normal subjects and from patients with various neuromuscular disorders. Studies on normal muscle indicated that no electrical activity can be recorded from completely relaxed muscle. With concentric needle electrodes action potentials of motor units can be recorded. These vary from 100 microvolts to 1 millivolt in amplitude and from five to ten milliseconds in duration. Action potentials of motor units are evoked by contraction and also by the mechanical stimulation incidental to insertion of the needle electrode. Concentric needle electrodes have strong directional properties. The recordable impulse from the action potential of the motor unit can be recorded in a range of 1 to 2 cm. This is considerably less than the theoretic distance at which this impulse should be recordable. The discrepancy is probably due to the directional properties of the electrode. No electrical activity can be recorded from a muscle whose nerve supply has been blocked by a local anesthetic. No simple relation is present between the activity of the motor unit and the degree of muscle tone. The factors concerned in the lack of correlation include (1) the intravascular and extravascular fluid within the muscle sheath; (2) rheologic properties of the muscle; (3) motor unit activity within the muscle with the nervous system intact, and (4) motor unit activity within the muscle with the nervous system damaged or destroyed. These factors are further subdivided.

Weddle, Feinstein and Pattle found in denervated muscle repetitive action potentials when the muscles were at approximately blood temperature. Fibrillary action potentials were of two types—potentials due to mechanical insertion of the needle electrode and rhythmically repeating potentials, presumably due to chemical stimulation. Fibrillations appear after denervation after a longer interval in man than in animals, and the interval depends on the muscle denervated. Thus, fibrillations occur from the tenth to the twelfth day in the sacrospinalis muscle and from the sixteenth to the eighteenth day in limb muscles. Eighteen years after denervation fibrillation potentials were obtained. In partially denervated muscles fibrillations can be obtained, the degree of difficulty in obtaining these potentials depending on the number of denervated motor units. In certain cases in which the lesion is presumed to be the result of axonal interruption fibrillation action potentials cannot be elicited. This may occur when the disease process involves the muscle fibers, the muscle fibers have undergone morphologic changes or the interruption of the axon has not occurred but, instead, the process is one of reversible ischemic block. Cooling denervated muscle decreases the number of fibrillations, whereas warming the muscle increases the activity. Administration of neostigmine increases.

the fibrillations. No correlation existed between the number and frequency of fibrillations and the degree or rapidity of muscular atrophy. The application of adequate physical therapy to denervated muscle results in maintaining vigorous fibrillation, whereas untreated denervated muscle fibrillates feebly. In cases of ischemic block which is reversible insertion potentials can always be elicited, and a few repetitive motor unit action potentials are usual.

In reinnervated muscles Weddle, Feinstein and Pattle found a decrease in the number of fibrillations occurring before the return of motor unit activity, and after the disappearance of fibrillation attempts at voluntary movement produced motor unit action potentials. This activity appears first near the point of entry of the nerve into the muscle. These potentials are at first of small amplitude but later become of greater amplitude and duration in reinnervated muscle than in normal muscle. Functional recovery is not detectable at the time that motor unit electrical activity first appears, and the time interval depends to some extent on the muscle involved. Reinnervated muscle presents small, highly polyphasic motor unit action potentials, and this type of activity is of diagnostic importance. From their data, the authors believe that neostigmine may facilitate neuromuscular transmission in the early stages of reinnervation. In the early stages of motor neuron disease the electromyographic picture resembles that produced by neostigmine in normal muscles, and similar changes are seen with progressive lesions of peripheral nerves. It is probable, therefore, that in the course of degeneration of a peripheral motor neuron there is a stage in which the myoneural junction threshold becomes decreased so that spontaneous contractions occur.

FORSTER, Philadelphia.

Psychiatry and Psychopathology

PSYCHOTHERAPY OF ALCOHOL ADDICTION IN A PRIVATE MENTAL HOSPITAL.

JAMES H. WALL, Quart. J. Stud. on Alcohol 5:547 (March) 1945.

The treatment described by Wall for addiction to alcohol is similar to that given most patients who are hospitalized for personality disorders. The patients were urged to accept as much responsibility and freedom as was possible. When a stabilizing situation in either the home or the business arose, the patient was encouraged to visit the home and resume his work. During the course of therapy, the family was given an opportunity to learn the psychologic forces involved and the methods of handling the patient.

Significant factors appeared in the study of 200 alcoholic patients. Over one-half had alcoholic relatives. Identification with them, however, seemed to be of greater importance than heredity. The men patients commonly experienced pampered, overprotected and spoiled maternal handling. The father frequently was a successful, forceful and aggressive person of whom the patient generally had a lifelong fear. Patients identified themselves with the mother, made poor sexual adjustments and acquired a feminine approach to life.

The women patients had no such familial or parental pattern but were prone to display terrific tantrums, which continued long after infancy. They commonly experienced dysmenorrhea and severe premenstrual depressions, which, no doubt, represented a resentment reaction against their femininity.

BECK, Buffalo, N. Y.

GROUP PSYCHOTHERAPY OF ALCOHOL ADDICTION. ROBERT G. HEATH, Quart. J. Stud. on Alcohol 5:555 (March) 1945.

Although prealcoholic personalities differ basically, a few common elements are apparent. There is a desire for supremacy with self pampering, which is associated with a wish to be sheltered and to avoid responsibility. As a result

of these trends, the person finds it necessary to withdraw from society, developing what the author calls "isolationism."

A psychotherapeutic approach was adopted which was similar to that of Alcoholics Anonymous. This treatment was considered to consist of two phases: (1) establishment of intellectual insight into the problem; (2) neutralization of the need for supremacy in order to remove the isolationism.

It was felt that real psychotherapeutic value was achieved by the opportunity given the alcoholic patient to expose his abnormal narcissistic personality traits. An acceptance of religion helps him combat frustration. The results of this type of treatment have been encouraging.

BECK, Buffalo, N. Y.

ALCOHOLIC HALLUCINATORY STATES. JACOB P. NORMAN, *Quart. J. Stud. on Alcohol* 5:563 (March) 1945.

Norman reviewed 292 cases of so-called alcoholic hallucinosis. In approximately one third of the cases in which this diagnosis was made on admission a rediagnosis of chronic hallucinosis, schizophrenia or manic-depressive psychosis was made later. A more adequate history of the prepsychotic personality might have assisted in early diagnostic accuracy.

The case material suggested to the author that a psychosis in a young, introverted alcoholic addict often produced a schizophrenic-like reaction, with a poor prognosis. Excessive drinking by an extroverted person, on the other hand, may produce a manic-like psychosis with a favorable outlook.

Electroshock treatment appeared to have been of limited value.

BECK, Buffalo, N. Y.

ANOREXIA NERVOSA, WITH SPECIAL REGARD TO INSULIN THERAPY. D. C. WILSON, DOROTA RYMARKIEWICZOWA and W. M. WHITE, *South. M. J.* 39:408 (May) 1946.

Wilson and his associates studied 10 patients with anorexia nervosa. The results with the Rorschach tests could practically be superimposed, one on the other, as the responses were practically identical. They indicated immaturity and suggested that the emotional development of these patients was checked at puberty. Deep insulin shocks were given to 5 of these patients until the habit of anorexia was broken. They gained weight, the appetite improved and they ate normally, but there was no fundamental personality change. When compared with the 5 patients in whom psychotherapy without shock was used, they seemed to be more deficient in insight at the time of discharge. This result seems to indicate that anorexia is not an incipient or mild form of schizophrenic reaction. Also, deep insulin shock may be used in cases of anorexia nervosa to check the refusal of food by the gastrointestinal system, but this must be followed by extensive psychotherapy if treatment is to be successful.

J. A. M. A.

PERSONALITY DEFECTS AND PSYCHIATRIC SYMPTOMS AFTER CEREBROSPINAL FEVER IN CHILDHOOD: MENINGOCOCCIC ENCEPHALOPATHY. M. NARASIMHA PAI, *J. Ment. Sc.* 92:389 (April) 1946.

Narasimha Pai studied 29 patients with residual neuropsychiatric symptoms after an attack of cerebrospinal meningitis in early life. The majority of the patients showed personality defects. They were backward in their studies and had difficulties of adaptation at school and, later, at work. They were unstable, dependent and restricted in their interests and showed tendencies to invalidism. The patients with a family history of instability showed severe and persistent reac-

tions after recovery from the cerebrospinal meningitis. Nearly all showed tendencies to neurotic breakdown under conditions of even moderate stress. Between complete recovery and advanced dementia there may be various grades of residual disability. A group of symptoms occurs with sufficient frequency to warrant the name of meningococcic encephalopathy. This syndrome consists mainly of changes in personality, intellectual deterioration, mild but prolonged depression, headaches and a pronounced tendency to invalidism.

J. A. M. A.

Diseases of the Spinal Cord

EFFECT OF FATIGUE, CHILLING AND MECHANICAL TRAUMA ON RESISTANCE TO EXPERIMENTAL POLIOMYELITIS. S. O. LEVINSON, A. MILZER and P. LEWIN, *Am. J. Hyg.* **42**:204 (Sept.) 1945.

Levinson and his associates found that monkeys subjected to exhausting exercise or to chilling during the incubation period of experimental poliomyelitis showed a higher incidence of, and severer, paralysis than the controls. Monkeys subjected to trauma of one or more limbs during the incubation period of experimental poliomyelitis showed no correlation with the location of the paralysis, and the paralysis did not differ in severity or extent from that in the controls. The incidence and severity of paralysis was significantly greater in monkeys inoculated with the virus during the summer months.

J. A. M. A.

POLIOMYELITIS AND ACUTE GASTROINTESTINAL UPSETS. W. R. KOVAR, Nebraska M. J. **30**:394 (Nov.) 1945.

Kovar observed an acute clinical condition with symptoms and signs similar to those of the preparalytic stage of acute anterior poliomyelitis. The condition made its appearance during the epidemic periods of poliomyelitis in Nebraska and in the years of severe drought and economic depression. There were fever, drowsiness, headache, pain and slight rigidity of the neck, pain and some rigidity of the spine and pain in the legs. The spinal fluid was normal. The author concluded that the condition was gastrointestinal in origin and that the preparalytic symptoms of poliomyelitis were the result of deficiency in the vitamin B complex. He describes 3 typical cases and stresses that acute toxic gastrointestinal upsets are capable of producing symptoms similar to those of the preparalytic stage of poliomyelitis, due basically to deficiency in the vitamin B complex and subclinical acute beriberi. All patients with simple acute gastrointestinal conditions encountered during epidemic periods of poliomyelitis should be given large doses of the vitamin B complex. These substances are also indicated as an adjunct to treatment of all acute debilitating diseases, especially diarrheas. It is suggested that if tonsils are to be removed during the poliomyelitis season, a high intake of the vitamin B complex be insured both before and after operation. Many so-called abortive cases of poliomyelitis may be in reality an acute gastrointestinal condition characterized by symptoms of avitaminosis B. The vitamin B complex plays an important part in the etiology of poliomyelitis, and the nutritional aspect of poliomyelitis should be thoroughly investigated.

J. A. M. A.

FIBROTIC TUBERCULOSIS OF THE CAUDA EQUINA. T. ALAJOUANINE and R. THUREL, *Rev. neurol.* **77**:155 (May-June) 1945.

Alajouanine and Thurel state that they have been unable to find a case similar to theirs in the literature. A woman aged 50 became ill in 1940 with pain in and

hyperalgesia of the left big toe. About two years later she complained of pain in the left heel, with gradual radiation up to the buttock and the lumbar region on that side. During March 1943 she had a febrile episode with exacerbation of pain. This was followed by remission except for the persistence of pain in the left large toe. During September 1944 she again became worse. This time the pain was noted especially anteriorly in the region of the lumbar dermatomes. During December 1944 motor weakness appeared and progressed rapidly; on Jan. 26, 1945 the left lower limb was almost completely paralyzed except for some movement of the toes. The knee and ankle jerks and the plantar reflexes were not elicited on the left side; there were sensory changes on the left from the third lumbar to the fifth sacral dermatome. There were also sphincteric disturbances. Examination after injection of iodized poppyseed oil showed no block. There were 46 lymphocytes per cubic millimeter in the spinal fluid; the Pandy reaction was positive; the protein was increased, and the Wassermann reaction of the fluid was negative. A laminectomy was done on Feb. 9, 1945 at the level of the second, third and fourth lumbar vertebrae. The roots of the cauda equina on the left side were observed to be enmeshed in fibrous tissue; the roots could not be separated. Biopsy of the fibrotic tissue showed tuberculosis. Operative intervention had no effect on the course of the illness.

N. SAVITSKY, New York.

SCHISTOSOMIASIS OF THE SPINAL CORD. C. GAMA and J. MARQUES DE SA, *Arq. de neuro-psiquiat.* 3:334 (Dec.) 1945.

Gama and Marques de Sa report the case of a white man aged 42 who became ill with fever and a grippal syndrome, which lasted about a month. Gonococci were identified on prostatic massage. The patient was given about 600,000 units of penicillin, after which he began to complain of pain in the lumbar, pleural and abdominal regions and of formications in the lower limbs. Eight days after onset of the pains he became paraplegic, with retention of urine and feces. On admission to the hospital, he was paraplegic; the knee and ankle jerks and the abdominal, cremasteric and plantar reflexes were all absent. There was diminished sensation for pain and temperature in the lower limbs; touch and deep sensibility were spared. The Wassermann reaction of the blood was negative. There were 16 per cent eosinophils in the blood. The sedimentation time was 6 mm. in three hours. Lumbar puncture revealed partial block and xanthochromia. There were 216 cells per cubic millimeter in the spinal fluid, 95 per cent of which were lymphocytes; the total protein was 80 mg. per hundred cubic centimeters. Injection of iodized poppyseed oil showed some stoppage at the sixth thoracic and a more complete level at the twelfth thoracic dermatome. Later repetition of injection of the iodized oil showed complete block at the second lumbar segment. A laminectomy was done at the level of the first, second and third lumbar vertebrae, and an intramedullary tumor was observed. Microscopic examination showed it to be a granuloma containing eggs of *Schistosoma mansoni*; there were areas of necrosis in the granuloma and many eosinophils among the infiltrating cells. The patient was given antimony and roentgen therapy. Three weeks after the operation he began to move his toes, and there was some return of sphincteric control.

N. SAVITSKY, New York.

CYSTIC HEMATURIC FORM OF POLIOMYELITIS. F. ALBERT, R. J. ABUIN FIGUEROA and M. BLANCO, *Semana méd.* 52:343 (Aug. 30) 1945.

Hematuria complicating poliomyelitis has been previously reported only in the preagonal stage. Albert and his collaborators observed hematuria in several

patients during the 1942 epidemic. Patients with hematuria presented also paraplegia of the legs, alone or associated with paresis of the arms. The consequent atrophy of the legs was severe. The patients did not have dysuria or renal or gastrointestinal disorders. The course of the neuromuscular lesions was not influenced by the hematuria. The general condition of patients in the course of the hematuric phase was good. Hematuria as a complication of poliomyelitis occurred within the first month of the disease. The urine was normal except for the presence of blood. Some cases of hematuria were complicated by urinary retention. Catheterization in these cases was not followed by hematuria. The blood pressure was normal. In some cases hematuria reappeared after several days of normal urinary secretion. The prognosis is benign, as hematuria, both primary and recurrent, disappears spontaneously and without treatment. The authors believe that this form of hematuria depends on a selective localization of the poliomyelitis virus in nerve tissues which elicit a transient neurogenic reaction of the bladder, with consequent hematuria.

J. A. M. A.

Treatment, Neurosurgery

USE OF PENICILLIN IN THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM. J. LAMAR CALLAWAY, RAY O. NOOJIN, ARTHUR H. FLOWER, BEATRICE H. KUHN and KATHLEEN A. RILEY, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:110, 1946.

Data are presented on 100 unselected patients who had active neurosyphilis and were treated with penicillin. The patients had a positive Wassermann reaction of the spinal fluid, an increase in cells in the spinal fluid and/or an increase in the total proteins of the spinal fluid, together with clinical symptoms and signs. The series includes both white and Negro, private and ward, patients. Eighty-five patients were male; 15 were female. Eighty-two were white, and 18 were Negro. Seventy-eight of the patients were between the ages of 20 and 49 years.

All patients, regardless of the type of neurosyphilis, were treated experimentally with a total dose of 4,000,000 Oxford units of penicillin introduced intramuscularly in isotonic solution of sodium chloride over a ten day period. Sixty per cent of the patients showed clinical improvement associated with definite improvement in the spinal fluid findings; 31 per cent, clinical improvement alone; 4 per cent, improvement in the spinal fluid findings unassociated with clinical change, and 5 per cent, decided clinical deterioration with no improvement or progression in their spinal fluid findings. After treatment, 8 per cent of the total had negative Wassermann reactions of the spinal fluid.

The patients with no previous therapy apparently responded best to penicillin, while those with previous adequate chemotherapy showed the poorest response. Previous fever therapy given more than six months before penicillin therapy exerted no effect on the response to penicillin.

Febrile Herxheimer reactions were frequent, but there were no reactions necessitating the termination of therapy. Extreme care should be taken with patients who have concomitant cardiovascular syphilis, in order to prevent serious Herxheimer reactions.

Although no definite conclusions can be established, a favorable therapeutic trend is indicated.

"To paraphrase Stokes and his co-workers, we feel that the results with penicillin therapy will for the moment, in the limited period of observation, bear comparison with those of fever therapy. It has, in our experience, produced transformations, symptomatically and serologically, without serious reactions or serious

inconvenience to the patient. Its effect has been equal to or superior to those obtained by longer, more expensive, more reactive fever therapy, arsenotherapy or treatment with heavy metals. Combinations of fever with penicillin in varying schemes of treatment may prove more valuable than either alone."

GUTTMAN, Philadelphia.

AN ANALYSIS OF COMPLICATIONS ENCOUNTERED DURING THERAPEUTIC MALARIA.
HILTON S. READ, LAWRENCE I. KAPLAN, FREDERIC T. BECKER and MARK F. BOYD, *Ann. Int. Med.* **24**:444 (March) 1946.

The authors report observations on 300 patients who were subjected to malaria for the treatment of neurosyphilis. Seventy-five per cent of the patients had asymptomatic neurosyphilis and were in excellent physical condition. Although racial immunity, previous attacks of natural malaria and the recent return of some patients from hyperendemic areas necessitated a number of reinoculations with heterologous malarial strains, 211 patients finally completed therapy with *Plasmodium vivax* and 89 with *Plasmodium malariae*.

The usual clinical features of malaria, namely, anemia, lowered blood pressure, herpes simplex, gastrointestinal distress, muscular pain, cough and loss of weight, are not considered in detail because of their relative benignity and their constancy of appearance during active febrile disease.

Jaundice, edema, mild renal damage and neural syndromes are relatively common features of untreated malarial infection. Though they presented clinical problems during active therapy, none was followed by permanent sequelae.

Hepatitis with jaundice can at times be adequately controlled by intravenous injection of fluids and a diet high in carbohydrate and protein without necessitating the interruption of malaria; but in most cases such interruption is indicated, at least temporarily. With active treatment, no case of jaundice persisted more than fifteen days. Excessive corpuscular hemolysis in the absence of impaired hepatic function accounted for almost 50 per cent of the cases in which icterus developed. The accidental transmission of a hepatotoxic agent with the inoculation of plasmodia into the blood, observed in 2 instances in this series, may play an important role in the "malarial" hepatitis observed during the therapy of neurosyphilis. Recent studies of homologous serum jaundice as differentiated from catarrhal jaundice (infectious hepatitis) may clarify this observation in the future. The occurrence of the complication, however, in mosquito-inoculated patients attests, at least in some instances, to a more specific toxic effect of malaria on the liver. Predisposing hepatic damage by prolonged arsenical therapy or rare syphilitic involvement of this organ cannot readily be evaluated. The constantly positive results in cephalin flocculation tests in cases of malaria adds to the growing impression that this reaction is nonspecific.

Although the causes of edema during active malaria may be multiple, hypoalbuminemia is probably the precipitating factor in most cases. Three cases of edema, with no adequate clinical or laboratory etiologic explanation, are reported. The duration of edema did not exceed thirty days, and in most instances proper diet proved to be adequate therapy.

Episodes of albuminuria and hematuria during repeated malarial attacks may play a role in the production of chronic recurrent focal nephritis. Abnormal urinary findings improved spontaneously during malarial activity in almost 25 per cent of the cases in which they appeared and did not last longer than thirty-one days in any case once antimalarial therapy was instituted. Malaria is to be considered an etiologic factor in acute nephritis, 4 cases of which were observed in this series.

The neurologic and psychiatric manifestations of malaria due to *P. vivax* and *P. malariae* are relatively benign and readily amenable to antimalarial therapy. Two mental complications, one an agitated psychosis and the other an acute hallucinatory syndrome, may have been related to the administration of quinacrine (atabrine).

An unusual form of severe respiratory distress with cyanosis was observed in 2 instances. It was also found that bronchial asthma is greatly aggravated during malarial paroxysms. The authors describe unusual cases of purpura, herpes zoster ophthalmicus, urticaria, hyperlipemia, spontaneous splenic rupture and hypocalcemic tetany complicating malarial infection. Fatalities, the only 2 in this series of 300 malaria-treated patients, occurred in the last 2 cases.

Although it is recognized that the course of repeated paroxysms in therapeutic malaria differs from that of natural malaria interrupted early in its cycle by anti-malarial agents, the use of malaria therapy presents an opportunity for the clinical study of the diverse manifestations of a disease which, because of extensive military operations in hyperendemic areas, may occupy the national health stage for many years.

GUTTMAN, Philadelphia.

THROMBOSIS OF A CAVERNOUS SINUS TREATED WITH PENICILLIN AND HEPARIN.

ROBERT HENNER and EARLE G. RIDALL, *Arch. Otolaryng.* **41**:295 (April) 1945.

Henner and Ridall report the case of a young man who was brought into the hospital with herpes of the lips and nose, cellulitis of the nose and a mild acute infection of the upper respiratory tract. The infection spread rapidly, and on the second day of hospitalization a blood culture yielded a growth of *Staphylococcus aureus*. Thrombosis of the cavernous sinus developed, and by the third day the patient was stuporous. Treatment with sulfadiazine from the time of admission seemed to be ineffective. Penicillin therapy was instituted, with intravenous injection of heparin at intervals. By the fifth day improvement was noted. A blood culture on the seventh day of hospitalization yielded no growth of organisms. Motion of the right eyeball began to return, and by the twelfth day external ocular movements were normal. Penicillin therapy was discontinued on the seventeenth day, and by the forty-second day the patient was completely cured. The use of heparin seemed to enhance the availability of penicillin by increasing the coagulation time of the blood. The response to penicillin of this infection with *Staph. aureus* suggests the possibility of producing more cures in cases of other infections caused by sulfonamide-resistant organisms.

RYAN, Philadelphia.

APICAL PETROSITIS: MEDICAL AND SURGICAL MANAGEMENT IN CASES WITH AND WITHOUT COMPLICATING MENINGITIS. WILLIAM C. THORNELL and HENRY L. WILLIAMS, *Arch. Otolaryng.* **43**:393 (April) 1946.

Though they well recognize that each case must be approached as an individual problem, Thornell and Williams outline the medical and surgical management of cases of petrositis with or without complicating meningitis. Before operation on the petrous pyramid, the complicating meningitis should be well controlled and the patient in the best possible physical condition. The use of sulfadiazine in conjunction with penicillin is strongly advocated. Care should be exercised to maintain an adequate intake and output of fluids in the use of such large doses of sulfadiazine. Adequate alkalization must also be considered to prevent renal complications. Intrathecal administration of penicillin in cases of meningitis is a valuable adjunct to other means of administration.

Reliance on chemotherapy alone is dangerous. Because of the frequency of intracranial extension from apicitis, adequate drainage must be established when symptoms of involvement of the petrous pyramid develop in the presence of an

apparently adequately draining ear. Drainage of the suppurative foci in the petrous pyramid should be accomplished in two stages. The perilabyrinthine region should be first explored; then, if necessary, a complete apicectomy may be done, preferably by the Ramadier-Lempert technic.

RYAN, Philadelphia.

MIGRAINE: ITS TREATMENT WITH PROSTIGMINE BROMIDE. I. J. PATTON, Canad. M. A. J. **54**:588 (June) 1946.

Patton used neostigmine bromide in the treatment of 6 patients with histories of migraine of from eight to twenty-five years' duration. Two patients reported moderate improvement; 3, great improvement, and 1 declared it was "a miracle." One 15 mg. tablet of neostigmine bromide is dissolved in 1 ounce (30 cc.) of distilled water. The patient is instructed to take the drug three times daily, beginning with 1 drop and increasing each dose by 1 drop until she is taking 10 drops three times a day. After continuing on this dosage for one week, the patient drops to a maintenance dose of 10 drops twice weekly, and if signs of impending headache are noticed she takes an additional 15 to 20 drops.

J. A. M. A.

USE OF NEOSTIGMINE (PROSTIGMINE) IN SUBACUTE POLIOMYELITIS. C. J. FRANKEL and R. V. FUNSTEN, South. M. J. **39**:482 (June) 1946.

Frankel and Funsten report on 58 patients with subacute poliomyelitis between the ages of 6 months and 42 years. All the patients showed variable amounts of muscular spasm; 8 presented pronounced incoordination and 4 moderate incoordination. Eight patients had contractures or conditions in which joints could not be moved without undue force or pain. Oral administration of neostigmine bromide was disappointing and was discontinued. Neostigmine methylsulfate, given subcutaneously in doses of 1.5 to 2 mg. for adults and 0.5 to 1 mg. for children, proved effective. Forty-six patients (80 per cent) showed improvement to normal ranges of passive motion in from three to eighteen weeks of treatment. Seventeen patients (30 per cent) showed dramatic improvement in from one to four days. Twelve patients (20 per cent) showed little or no improvement. Twenty-three patients showed good results only after treatment was interrupted for from five to seven days and then repeated. All patients with muscular incoordination showed definite improvement. None of the patients had permanent contractures. The patients became ambulatory more rapidly, and the period of hospitalization could be cut down. The return of active muscular power did not seem to be influenced by the drug. Treatment with this drug can be, and probably should be, combined with modified hot pack therapy.

J. A. M. A.

SURGICAL TREATMENT OF VASCULAR ANOMALIES OF THE PREMOTOR AREA PRODUCING EPILEPSY. F. L. REICHERT, Surgery **19**:703 (May) 1946.

Fifteen patients were treated for epileptic seizures due to vascular anomalies in the premotor region. The follow-up period was at least five years. The treatment consisted in coagulation of the vascular lesions, and the results indicate that the procedure was feasible and satisfactory. Nine of the 15 patients had premotor signs. Six patients, besides having the cortical vascular anomalies, had one or more dural angiomas. Four patients had cortical angiomas or hemangiomas. Three were proved to have callosal angiomas by ventricular needle puncture. In these 3 cases of callosal angiomas the ventriculograms showed a new sign of separation of the bodies of the ventricles. Coagulation of the abnormal vessels frequently produced a transient hemiplegia until normal collateral vascular channels developed. Subtemporal decompression made a smoother convalescence if employed when there

was disturbance of cortical circulation resulting from coagulation. Intravenous injection of hypertonic solutions aided in overcoming the cerebral edema that followed the disturbance of circulation incident to the operative coagulation. Two of the 15 patients had only temporary relief from seizures; 7 had milder and less frequent attacks, and 6 had no seizures after operation.

J. A. M. A.

CARE OF THE PARAPLEGIC'S URINARY TRACT. M. H. NOURSE and H. C. BUMPUS, U. S. Nav. M. Bull. 46:1053 (July) 1946.

Consequent to trauma to the spinal cord, after a few months, the bladder wall thickens, there is a tendency toward spasticity of the musculature, and the mucosa shows increased trabeculation. Inadvertently, the bladder becomes overdistended, injuring the tone of the muscle, subjecting the bladder to trauma from overdistention in general surgical procedures and invariably leading to febrile reactions when catheterization at regular intervals is resorted to. The authors apply the same criticism to tidal drainage. In cases of battle casualties, in which various methods of transportation must be considered, a suprapubic drain is the only insurance against obstruction and infection. Much, however, favors the use of urethral drainage in civilian medicine or paraplegic centers, where adequate observation and nursing care are available.

The automatic bladder of infancy or injury to the cord is controlled via a reflex arc in the conus medullaris in the region of the twelfth thoracic and the first lumbar segment. Voluntary control of the bladder in adult life is the result of development of a pathway for the passage of inhibitory impulses from higher centers. Trauma to this pathway results after a few months in the development of an automatic bladder. There is a rough correlation between the height of injury in the cord and the resulting bladder function established. A more or less efficient automatic bladder may be expected from a high lesion in the cord, and in the case of a casualty in the lower lumbar region of the spine ultimate voluntary control is possible.

In the spastic bladder, the ability of the detrusor muscles to overcome the obstruction of spastic sphincters governs the satisfactory emptying of the bladder. Transurethral resection for the removal of this obstruction enables certain of both the automatic and the voluntary types of function.

Automatically functioning bladders were present in 37 of the 87 cases of paraplegic casualties among sailors and Marines in the authors' series. In 16 of these cases transurethral resection was necessary for efficient action. In the other 21 cases a minimal residuum of urine of not more than 2 ounces (59 cc.) may be present most of the time. Resection of the tissue of the neck of the bladder is reserved for cases in which the patient is unable to expel any urine or in which many ounces of residual urine remain. Streptomycin has been valuable in the control of infection with residual urine.

Voluntary control or initiation of micturition in cases of complete severance of the cord above the conus has not been observed, nor have the authors seen cases of conditioned reflexes in which the patient strokes his thighs and the bladder empties. By proper modeling of the muscles of the bladder neck through transurethral resection (29 cases), voluntary function was obtained with injuries below the conus.

Healing following resection is slow in cases of paraplegia, and late bleeding is often a complication.

Another complication in the care of the paraplegic patient is hypercalcinuria. Routine roentgenographic and cystoscopic examinations are necessary for discovery of stones because of the insensitivity of the urinary tract. An elevation of temperature is usually the first sign of calculus obstructing the tract. With preventive measures, which include large fluid intake, frequent change in position of the patient and acidification of the urine by means of mandelic acid, calculi in the upper part of the tract have been observed in only 14 of the 87 cases.

BERRY, Philadelphia.

POSTERIOR COMMISSURAL MYELOTOMY FOR TABETIC GASTRIC CRISES. J. CHRISTOPHE and J. GUILLAUME, *Rev. neurol.* **77**:78 (March-April) 1945.

Christophe and Guillaume treated a man aged 50 who had had gastric crises every year for fifteen years. The pupils showed mild mydriasis, with no reaction to light or in accommodation. The ankle jerk was absent. There was mild ataxia in the lower limbs. Prior to the operation he had had a severe crisis of about seven weeks' duration. The Wassermann reactions of the blood and the spinal fluid were negative. On June 28, 1944, a laminectomy was done at the level of the first to the fourth dorsal segments, inclusive. An incision was made into the cord strictly in the midline after separation of Goll's columns. The entire thickness of the cord was incised. The pain disappeared immediately after the operation. The patient had to be catheterized for a few days. For a short time he noted numbness of the feet. There was mild diminution of sensation for pain and temperature from the fifth to the seventh dorsal segment, inclusive; these sensory changes disappeared in a month. On Feb. 1, 1945, the authors stated that the "patient recently reported that the pain had not recurred." There were no new neurologic findings.

N. SAVITSKY, New York.

MENTAL CHANGES ACCOMPANYING ABORTIVE HYPERTHYROIDISM: TREATMENT WITH SHOCK. FLAVIA DE SOUZA, *Arch. brasil. de med.* **35**:199 (July-Aug.) 1945.

De Souza reports 2 cases in which mental symptoms accompanying hyperthyroidism cleared up after shock therapy. The first patient, a girl aged 16, presented evidence of hyperthyroidism, extreme emotional lability, ranging from exultation to depression, hypomanic behavior, insomnia, anorexia and bizarre mental content. Eight metrazol treatments were given, after which the mental symptoms cleared up. Treatment for her thyroid disturbance was continued after the mental symptoms disappeared. The second patient, a white woman aged 40, in addition to hyperthyroidism, presented the clinical picture of a depression, with suicidal ideas, indecisiveness, loss of interest, inability to work and feelings of mental insufficiency. She had been incapacitated for eight months because of the mental symptoms. Six metrazol treatments were given, and the mental symptoms cleared up. The author concludes that hyperthyroidism is not a contraindication to shock therapy provided there is no serious impairment of the circulatory apparatus. He adds that treatment for the hyperthyroidism should be continued after the shock therapy.

N. SAVITSKY, New York.

ACCIDENTS AND COMPLICATIONS OF CONVULSIVE THERAPY. E. ARRUDA, *Arq. brasil. de neurol. e psiquiat.* **25**:33 (Jan.-March) 1946.

Arruda refers to his own experiences but gives no statistics. He states that temporomandibular luxation is the most common complication of convulsive therapy and that it is due to very wide opening of the mouth. Luxation of the shoulder is due to sudden abduction and elevation of the arms. In 1 case in his series there was fracture of the lower jaw. There were no vertebral fractures. The author mentions cases of cardiovascular collapse which came on fifteen to twenty minutes after induction of the shock, with weakness, cold extremities, pallor and chills. He cites an unpublished case of a colleague in which a spinal hemorrhage developed after convulsive therapy. He reports a case of gangrene in the region of the antecubital fossa resulting from infiltration of metrazol into the tissues. In 1 case a burn occurred at the site of application of electrodes. Hyperthyroidism became

evident in 1 case after convulsive therapy (probably metrazol). He comments on the probability that terror or fear of injection may have precipitated the hyperthyroidism. The appearance of amyotrophic lateral sclerosis in a woman aged 40 after shock therapy is considered as having been due to the shock. Two cases of pulmonary tuberculosis are cited in which the disease became active after treatment. The author points out the value of roentgenographic examination of the chest before treatment. He does not approve of the use of curare, for it increases the risk and does not entirely prevent fractures. He describes a method of preventing dislocation of the jaw by placing one assistant at the patient's head with the palm of one hand against the chin, exerting pressure during the seizure, while the other hand keeps the gag from being pushed out by the tongue. He does not believe that a pillow placed beneath the patient prevents fracture of the vertebrae. In 1 case muscular twitching, which persisted for a few hours after a metrazol convulsion, cleared up with 2 cc. of "sommifene" (diethyl-diallyl barbiturate of diethylamine) administered intravenously.

N. SAVITSKY, New York.

TUBERCULOMA OF THE BRAIN: SURGICAL EXCISION. TOLOSA, TENUTO and DA SILVA JR., *Arq. de neuro-psiquiat.* 4:28 (March) 1946.

A single laborer aged 21 gave a history of jacksonian attacks on the left side and headaches of a few months' duration. Examination showed bilateral papilledema and weakness of the left side of the face. Lumbar puncture revealed an initial pressure of 40 mm.; the total protein was 40 mg. per hundred cubic centimeters. Ventriculographic examination revealed a tumor in the right frontoparietal region. At operation, performed on Oct. 20, 1944, three small tumors, the size of olives, were removed. Histologic examination revealed them to be tuberculoma. After the operation there were some accentuation of the facial weakness and dysstereognosis on the left side. On the sixth postoperative day the temperature rose. There was roentgenographic evidence of pulmonary tuberculosis. The patient died of pulmonary tuberculosis in June 1945. There was no recurrence of the cerebral lesions. Roentgenograms of the lungs were not obtained before operation. The authors note that tuberculomas can be operated on, like other tumors of the brain, if the general condition does not contraindicate such intervention.

N. SAVITSKY, New York.

PENICILLIN TREATMENT OF SIX PATIENTS WITH NEUROSYPHILIS WHO HAD HAD MALARIAL THERAPY. P. W. LONGO, M. ROBOTELLA and J. B. DOS REIS, *Arq. de neuro-psiquiat.* 4:47 (March) 1946.

The authors report their experience with penicillin in treatment of 3 patients with dementia paralytica, 2 patients with the tabetic form of dementia paralytica and 1 patient with neurosyphilis with convulsions. The minimum duration of the illness was one year; 1 patient had been ill five years and another ten years. Intrathecal injections were given every forty-eight hours, and 20,000 to 25,000 units of penicillin was administered intramuscularly every three hours. One patient received only intramuscular injections, with good results. In 2 patients the meningeal reaction was so severe that intrathecal injections had to be abandoned. Two patients had transitory confusion. One patient had severe convulsions during treatment, but convulsions were present before therapy was begun. Two patients exhibited notable improvement in behavior after treatment. One patient showed less irritability. For 3 other patients the results were inconclusive. In 1 case the total protein became diminished during treatment and precipitation in the first part

of the colloidal gold test became less pronounced, though the Wassermann reaction continued to be positive. Cellular responses to intrathecal injection of penicillin were noted in 2 patients.

N. SAVITSKY, New York.

PENICILLIN THERAPY OF SYPHILITIC ATROPHY OF THE OPTIC NERVE. P. W. LONGO and J. M. TAQUES BITTENCOURT, *Arq. de neuro-psiquiat.* 4:55 (March) 1946.

The patient, a man, began to find it difficult to distinguish colors in August 1944. In January 1945 he noted a definite decrease in visual acuity and in May could not recognize people at 3 meters. In August he had difficulty in reading. Examination on August 16 showed that the pupils were equal and regular and reacted in accommodation but not to light. There were primary atrophy of the optic nerves, diminished vision and ability to count fingers at 4 meters. The fields showed definite concentric contraction. The knee and ankle jerks were not elicited. The spinal fluid was clear, with 48 cells per cubic millimeter, of which 10 per cent were monocytes and 90 per cent lymphocytes. The Wassermann reaction of the spinal fluid was positive. Treatment was begun on August 17 and was continued for eleven days. The total dose was 2,500,000 Oxford units of penicillin; 20,000 units was given every hour intramuscularly. During the first two days 20,000 units was given intrathecally every day. From the third to the ninth day the dose was increased about 10,000 units per day. Lumbar puncture was done daily during treatment. There was no increase in pressure; the total protein and the cell count were slightly increased, especially the monocytes. Thirty days after treatment the total protein was decreased and the Pandy and Wassermann tests were less positive. Visual acuity improved from 0.1 to 0.15. The visual fields became definitely wider. The achromatopsia persisted.

N. SAVITSKY, New York.

INTRATHECAL PENICILLIN THERAPY: IMMEDIATE AND LATE REACTIONS. J. M. TAQUES BITTENCOURT, J. A. CAETANO DA SILVA JOR and H. M. CANELAS, *Arq. de neuro-psiquiat.* 4:68 (March) 1946.

The authors report complications of intrathecal injection of penicillin in 17 cases of syphilis, 11 cases of dementia paralytica, 2 cases of tabes, 2 cases of syphilitic optic neuritis, 1 case of syphilitic myeloradiculitis and 1 case of syphilitic osteitis. The penicillin was given suboccipitally in 14 cases and by the lumbar route in 3 cases. It was given daily in all cases, beginning with 20,000 units and increasing by 10,000 units per day up to a dose of 100,000 units in each injection. The total dose administered intrathecally varied from 250,000 to 700,000 units. Each patient had eight to eleven injections. The immediate reactions were as follows: (1) sensations of heat, and more rarely of cold, in the parietotemporofrontal region in all cases in which the injections were given suboccipitally; (2) fleeting headache, usually frontal, in all such cases, and (3) vomiting and nausea in 35 per cent of the total series of cases. The usual late reactions were: (1) lumbar radicular pain, lasting a few hours after the injections, in all cases in which the lumbar route was used; (2) frontal headaches, lasting more than four hours, in 30 per cent of all the cases, and (3) an increase in temperature to 38 C. (100.4 F.) for a few hours after injections in 12 per cent of the cases. Rare late reactions were: (1) diffuse perspiration, changes in pulse, visual disturbances, torpidity and even loss of consciousness, in 3 cases; (2) fine tremors, especially in the upper limbs, lasting about an hour, in 2 cases; (3) delirium with visual hallucinations and motor agita-

tion, in 1 case, and (4) a cauda equina syndrome with perianal anesthesia and sphincteric disturbances, lasting over a month, in 1 case. The worst reactions were noted with doses of more than 50,000 units. No relation was observed between the reactions and the duration of the penicillin therapy. The authors believe that impurities in the penicillin preparation were a factor in some of the reactions.

N. SAVITSKY, New York.

SURGICAL TREATMENT OF PAIN OF THE TRIGEMINAL NERVE: RETROGASSERIAN NEUROTOMY BY TEMPORAL INTRADURAL ROUTE. J. RIBE PORTUGAL, Hospital, Rio de Janeiro 29:501 (April) 1946.

Ribe Portugal divides surgical operations on the trigeminal nerve into four groups: (1) on the peripheral branches, (2) on the gasserian ganglion, (3) on the dorsal roots and (4) on the cerebral trunk. He describes an incision giving access to the trigeminal nerve at the pons Varolii. He explains his technic for sectioning the trigeminal nerve by the temporal intradural route, that is, by opening the dura, elevating the temporal lobe and opening Meckel's cavity or sectioning the tentorium. He prefers opening Meckel's cavity because the tentorium supports the cerebrum. Both operative procedures are easy, avoiding trauma of the gasserian ganglion and not provoking bleeding. He presents 20 illustrative case histories from among the 118 cases in which he sectioned the trigeminal root by the temporal and subtentorial approach.

J. A. M. A.

EFFECT OF SYMPATHECTOMY ON PHANTOM PAINS AFTER AMPUTATION OF LIMBS. A. ELLONEN, *Acta chir. Scandinav.* 93:131, 1946.

Ellonen reports 28 cases of phantom limb pain in persons who had an extremity removed. Phantom limb pain followed amputation of the femur in 10 cases, amputation of the leg in 14 cases, amputation of the foot in 2 cases and amputation of the arm in 2 cases. Sympathectomy or blocking of the sympathetic nerves was performed in 15 of these cases. Spinal anesthesia was administered in the remaining 13 cases. In 5 cases of permanent phantom limb pain ("absolute cases") complete disappearance of pain resulted from lumbar sympathectomy, and in an additional case, from cervical sympathectomy. In 1 case lumbar ganglionectomy, blocking of the sympathetic nerve and resection of the sciatic nerve proved ineffective, while disappearance of pain resulted from repeated spinal anesthesia. In 6 cases definite recovery from temporary phantom limb pain ("relative cases") resulted from blocking the sympathetic nerve. Blocking was obtained with 30 cc. of a 1 per cent solution of procaine hydrochloride. Spinal anesthesia was administered in 12 cases and proved ineffective in all.

J. A. M. A.

SURGICAL TREATMENT OF SCLERODERMA. M. HÄMÄLÄINEN and B. SÖDERLUND, *Acta chir. Scandinav.* 93:201, 1946.

Hämäläinen and Söderlund report 4 cases of scleroderma in which sympathectomy was carried out at the district hospital of Kuopio, Finland. The patients were a man aged 28, 2 women aged 38 and a girl aged 12 years. The follow-up time in these cases was one and one-half years. The results have so far been satisfactory. It is concluded that scleroderma should not be considered an incurable disease and that surgical treatment is warranted. Disturbances of calcium metabolism were not present in these cases. Sympathectomy is to be preferred to parathyroidectomy, which is associated with greater risk.

J. A. M. A.

Muscular System

PRIMARY MYOPATHY CHARACTERIZED BY "MICROPYGIA" IN THE FIRST GENERATION AND SCAPULOHUMERAL DYSTROPHY IN SECOND ONE OF CONSANGUINEOUS PARENTS. S. MATUS, South African M. J. **20:170** (April 13) 1946.

Matus reports the occurrence of familial primary myopathy in a man aged 46 and in his 2 sons, aged 5 and 6 years respectively. The 2 children presented a muscular atrophy of the pure scapulohumeral type. The supraspinous and infraspinous fossae were nearly devoid of any muscle, and the spine of the scapula was forming a visible ridge under the skin. The deltoid and the pectoral muscles were involved. The manifest atrophy of the serratus contributed to the "winged scapulas" and gave to the children a peculiar attitude, conspicuous by the "dropped shoulders" and the protruding abdomen. A scoliotic spine completed the clinical picture. The father of the 2 boys presented an unusually small buttock with pronounced atrophy of the gluteal muscles, for which the term "micropygia" was coined by the author. The smallness of the buttock was accentuated by the adiposity above (pseudo-hypertrophy of the upper part of the gluteal muscles). The collateral history of the man revealed that his cousin, the daughter of the middle-aged brother of his father, had the same "micropygia." The familial origin of this muscular dystrophy was further evidenced by the fact that his wife is his cousin, the daughter of the youngest brother of his father, while he is the son of the oldest brother.

J. A. M. A.

MYOTONIA CONGENITA (THOMSEN'S DISEASE): THERAPEUTIC CONSIDERATIONS. P. PUPO, J. G. MEIRA and J. NASSER, *Arq. de neuro-psiquiat.* **4:1** (March) 1946.

The authors report studies on a Brazilian aged 21 of Italian descent, with no family history of nervous or mental disease. The diagnosis of myotonia congenita was definite, the illness having been present since the seventh or eighth year of life. There was no involvement of the cardiac or the ocular muscles. Electrical reactions and the electromyographic and ergographic findings were typical of the disease. On two occasions, thirty days apart, twenty minutes after the intramuscular injection of 1 cc. of solution of epinephrine hydrochloride myotonic reactions almost disappeared for about twenty-five minutes. Intramuscular injections of suspension of epinephrine in oil had no effect. Intravenous injections of 0.25 mg. of atropine sulfate in 10 cc. of 25 per cent dextrose had no effect on the myotonia. The oral administration of ergotamine tartrate for six days had no effect. One gram of quinine sulfate by mouth began to have an effect on the myotonia in twenty-five minutes. The myotonia disappeared completely in forty to forty-five minutes. Myotonia was absent for an average of ten hours in eight such experiments. The effects of quinine were demonstrated by moving pictures and electromyographic and ergographic studies.

N. SAVITSKY, New York.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Kenneth J. Tillotson, M.D., *Presiding*

Regular Meeting, April 18, 1946

Comparison of Epileptic Patients with Normal Electroencephalograms with Those with Abnormal Electroencephalograms. DR. JOHN A. ABBOTT.

This study is based on a group of 193 persons attending the clinic for adult epileptic patients at the Massachusetts General Hospital. As criteria for inclusion in this group, the clinical diagnosis of epilepsy was unequivocal and the electroencephalogram was taken in accordance with a well standardized procedure. Of these 193 patients, 40, or 21 per cent, had normal electroencephalograms; 20, or 10 per cent, borderline patterns, and 133, or 69 per cent, abnormal patterns.

Comparison of patients having normal electroencephalographic patterns with those having abnormal patterns revealed the following differences:

1. In general, the age of onset of chronic epilepsy was higher among patients of the first group, with normal electroencephalographic patterns, than among those of the second group, with abnormal patterns.

2. The incidence of patients having grand mal without any other type of seizures was strikingly higher in the first group than in the second group.

3. In general, seizures were less frequent among patients of the first group than among patients of the second group, with a high incidence of patients in the first group who had only one or two seizures a year.

4. Analysis of medication at the time of the last visit showed that for all kinds of anticonvulsant drugs the dose was slightly, but consistently, smaller for patients of the first group than for patients of the second group. Furthermore, at the time of the last visit, 7, or 18 per cent, of the first group had discontinued all such medication without recurrence of seizures, whereas only 2 or 3 per cent of the second group could discontinue medication.

5. Five, or 13 per cent, of the patients in the first group reported that all, or all but one, seizure occurred in sleep, whereas this was true for only 2 or 3 per cent of the patients in the second group.

6. With respect to a history of seizures in infancy or childhood, there was only a slight difference in favor of the first group, with 10 per cent of the first group and about 16 per cent of the second group showing such seizures.

7. With respect to established post-traumatic or other encephalopathy, there was, again, only a small difference in favor of the first group, with 30 per cent of the first group and about 35 per cent of the second group showing established encephalopathy other than cerebral dysrhythmia.

8. Eighteen per cent of the first group and about 26 per cent of the second group gave a positive family history for epilepsy.

9. With respect to scholastic and occupational histories, there was a considerable difference between the two groups. Of the first group only 10 per cent, whereas of the second group about 29 per cent, had experienced serious scholastic or occupational difficulties.

DISCUSSION

DR. STANLEY COBB: This is an interesting and valuable paper. All who manage epileptic patients are asked: What does it mean when a person with known epilepsy has a normal electroencephalogram? That is, the record is normal when made between attacks, but it should be emphasized that the pattern would have been abnormal during an attack.

Dr. Abbott has shown that the patients with abnormal electroencephalograms are likely to have an earlier onset of the disease, more and severer seizures and convulsions rather than petit mal attacks, and that they need more medicine to keep them free from seizures. Is there any chance that the patients having had more medicine might have made the electroencephalograms more abnormal?

In summarizing, Dr. Abbott remarked that a history of fits in infancy was rare with a normal electroencephalogram. The association was less common, but I do not think that it was rare. There is perhaps a lesson to be drawn from the slide showing that patients with abnormal tracings needed more medicine. Is one to conclude that medication can be stopped when the electroencephalogram becomes normal? That is a hard thing to decide.

DR. WILLIAM G. LENNOX: I endorse Dr. Cobb's statement that this is a worth while piece of work. Many clinicians expect every patient who has seizures to have abnormal brain waves. Perhaps the electroencephalogram was oversold at first.

I wish to commend Dr. Abbott for keeping the work within practical limits. Several years ago Dr. and Mrs. Gibbs and I listed comparable data for 1,000 patients, data which we have yet to tabulate. Dr. Abbott has presented various factors which have to do with records which are normal or abnormal. One might try to break down these factors a bit.

First, I raise the question of what constitutes an abnormal record. Dr. Abbott, probably wisely, did not try to define the normal. Recently I have been nonplused by the number of epileptic persons with normal records. Dr. and Mrs. Gibbs and I found that 16 per cent of epileptic patients examined at the Boston City Hospital had normal records. For the last 500 patients I examined at my private laboratory this proportion was 25 per cent. Perhaps private patients are better endowed with respect to their brain waves, have had less cerebral damage or have had epilepsy a shorter time, or perhaps our conception of what is normal has become more liberal.

Another factor is age. Is it age per se, or the fact that older patients have less frequent seizures? It is known that the older person, whether ill or normal, has more stabilized brain waves than the younger one. Perhaps an epileptic patient has more normal brain waves as he gets older whether he is treated or not. It is known that seizures become more infrequent as a person grows older; perhaps brain waves become more normal. We have evidence on the influence of seizures in records made on identical twins, only 1 of whom has epilepsy; that one twin has more abnormal brain waves than the nonepileptic co-twin. There is difficulty in drawing conclusions based on tabulation of the total number of seizures. Patients with petit mal have so many seizures that any average figures are distorted.

Dr. Abbott did not classify his results with respect to the degree of abnormality and the various types of electroencephalographic records. That, perhaps, would be interesting. The degree of abnormality is important with respect to the severity of the epilepsy. There, again, is a difficulty, in that patients with petit mal have a much higher incidence of abnormality in the electroencephalogram than patients with other types of seizures. That is partly because overventilation usually brings out the alternate spike and wave pattern in patients subject to petit mal.

I wonder whether Dr. Abbott would sum up the data from his last chart by saying that an epileptic patient with normal brain waves has a relatively good prognosis.

DR. ROBERT S. SCHWAB: I congratulate Dr. Abbott on his turning an unfavorable aspect of the situation into an advantage. When my colleagues and I found that 15 to 20 per cent of electroencephalograms in cases of proved epilepsy were normal, it was embarrassing to explain this to the clinician. It was not mentioned at meetings unless necessary; one was somewhat ashamed not to have the results of the examination 100 per cent in agreement with the clinical findings, like the Wassermann test for syphilis or the roentgenographic examination of the chest for tuberculosis. So many laboratories have arrived at approximately the same percentage that we have accepted it as correct.

The clinician can be informed that the patient with a normal electroencephalogram is better off than the patient with an abnormal record. He may still have epilepsy, but he has a better chance to get along; and, as Dr. Abbott has shown, he has a better chance of discontinuing medication and remaining free of seizures. Perhaps, therefore, this disadvantage of having a laboratory test that was only 80 per cent in agreement with the clinical evidence can be turned to a distinct help to the patient.

The fact that a normal electroencephalogram indicates fewer seizures, and those mainly at night, better response to anticonvulsant drugs and, finally, ability to secure employment and hold jobs is a definite prognostic advantage to any patient.

DR. MILTON GREENBLATT: I was interested in Dr. Abbott's report. I wonder whether the patients were classified according to possible factors precipitating the seizures. Some patients have convulsions in the hypoglycemic state; some, after overindulgence in alcohol, some, after a period of insomnia, fatigue, exertion or emotional upset. Would an analysis on the basis of these factors have revealed any difference in the incidence of electroencephalographic abnormality? For instance, if the seizures were customarily precipitated by drugs or hypoglycemia, would the electroencephalograms have been more abnormal than if the seizures were not dependent on any known physiologic stress or intoxication of the nervous system?

At the Boston Psychopathic Hospital, my associates and I recently analyzed cases of seizures due to rum intoxication, selecting only patients whose seizures were entirely dependent on alcoholic overindulgence and who never had seizures prior to the onset of heavy drinking and did not have a family history of fits or convulsions. The electroencephalograms were surprisingly normal.

We have also seen 2 or 3 cases of seizures occurring in the acute withdrawal phase of barbiturate poisoning. The electroencephalograms were normal.

The problem as to whether the clinical findings correlate with the electroencephalographic abnormality always implies the converse, whether the electroencephalographic abnormality correlates well with clinical findings. If a patient has an abnormal electroencephalogram, does that signify he is more likely to have epilepsy now or later? From my work with Dr. S. Levin in cases of neurosyphilis, I am convinced that the more abnormal the electroencephalogram, the greater the chance of finding seizure-like phenomena in the histories of patients with neurosyphilis.

DR. JOHN ABBOTT: Dr. Cobb has asked whether the larger amount of medicine taken by patients with abnormal electroencephalograms might increase the abnormality of the tracing. The answer would appear to be "No." Goldman and Schwab concluded, from independent studies, that patients to whom anticonvulsants were administered showed improvement in the epilepsy and in the electroencephalogram

pari passu with the passage of time. Lennox and Gibbs showed that the electroencephalographic pattern improved immediately with appropriate intravenous doses of certain anticonvulsants.

Dr. Cobb also observes correctly that among patients with normal electroencephalograms fits in infancy should hardly be called "rare" but can be described, at least for this series, as rarer than among patients with abnormal electroencephalograms. That is, with respect to fits in infancy the two groups of patients overlap, and there is a difference in favor of the group with normal electroencephalograms. This overlapping of the two groups, with a difference in favor of the group with a normal electroencephalogram, was a feature of almost every comparison of the two groups.

Dr. Cobb asks about the indications for withdrawal of medication. That so many patients (7 of 40) with normal electroencephalograms had stopped medication came as a pleasant last minute surprise, and there has not yet been time to analyze these 7 cases in detail. It is to be hoped that from this analysis, which is to be undertaken, there will emerge criteria other than the occurrence of a normal electroencephalogram which will have prognostic value with respect to the withdrawal of anticonvulsants.

As an intelligence test, the presentation of the first slide was too hurried to be fair, and those who failed the test need not feel embarrassed. This slide showed the age at the time of electroencephalographic recording for each of the 40 patients with normal patterns and for each of 38 patients with abnormal patterns. The group of 38 patients was constructed by seeking for every patient who at a certain age had a normal electroencephalogram a corresponding patient who at the same, or nearly the same, age gave an abnormal record. For every patient who gave an abnormal pattern at the age of 35 or less, it was possible to find a patient who had given an abnormal electroencephalogram at the same age. For patients between the ages of 36 and 72, this exact matching was not possible, but the average age was the same for patients in this age range who gave normal and for patients who gave abnormal electroencephalograms. For the 2 oldsters who had normal electroencephalograms at 73 and 75 years of age, respectively, there could be found no corresponding patients who gave abnormal electroencephalograms at even approximately these ages; hence, in the selected group of patients with abnormal electroencephalograms there are only 38 patients, or 2 less than the group of 40 patients with normal electroencephalograms. This matching, simple in fact but complicated in description, was undertaken in order to correct for factors due to age differences between patients with normal and patients with abnormal electroencephalograms.

Dr. Lennox asks about the criteria used in classifying records as normal or abnormal. Briefly, they were as follows: (1) symmetry, as against asymmetry; (2) a predominance of activity faster than 8 per second, as against activity slower than 8 per second; (3) absence, as against presence, of paroxysmal runs of any but normal alpha activity; (4) absence, as against presence, of single waves slower than 8 per second and higher in voltage than the predominant 8 per second or faster activity; (5) freedom from disturbance, as against slowing, during the first or second minute of overbreathing in a nonfasting state.

It is reassuring to learn that Dr. Lennox found normal electroencephalograms among 25 per cent of the epileptic patients studied in his private laboratory. It is a familiar fact that the incidence of abnormal electroencephalograms varies immensely with the "normality" of samples from the normal population, and one might well expect such variation in samples from the epileptic population. When, in 1941 or 1942, my colleagues and I first got normal electroencephalograms in about 20 per cent of epileptic patients, at a time that others were reporting 16 per

cent or less, we were disconcerted and decided to start all over again. This paper has been a product of our second start, and we find ourselves now in the best of company. Our head technician is a Scotchwoman, and she approves of our findings, so that even the factor of Scottish descent in recording and interpretation has been allowed for.

As to the factor of age, about which Dr. Lennox speaks, I hope that the more detailed account of the first slide just given will meet some of his valid criticism.

With respect to differences between the two groups on the basis of the types of seizures, notably petit mal as opposed to grand mal, some answer to Dr. Lennox' again valid criticisms may follow from a review of the slide showing analyses of the two groups for types of seizures. In each group the percentages of patients presenting petit mal and those presenting grand mal seizures were about the same. However, 30 per cent of the group with normal electroencephalograms had grand mal alone, without any other type of seizure, and only 15 per cent of those with abnormal records had grand mal alone. This still leaves open the possibility that the higher frequency of seizures among patients with abnormal electroencephalograms may be due to the greater prominence of petit mal seizures among such patients. Dr. Lennox' comments in this connection point the direction for further investigation.

In answer to Dr. Lennox' question about prognosis, it would appear from this study that a normal record between seizures is prognostically favorable, but only "favorable." It does not preclude occasional seizures despite the most liberal exhibition of anticonvulsant drugs.

Dr. Greenblatt asks about external precipitants of seizures and the relation of vulnerability to such precipitants and the character of the brain wave record. This question also points the direction for further study. In the work of other investigators there is much to indicate that the patient with an abnormal electroencephalogram is more vulnerable to the factors which may cause seizures than is the patient with a normal electroencephalogram. But this study, at least as far as it has been carried, does not contribute an answer to this interesting question.

Methylphenylethyl Hydantoin ("Mesantoin") and Trimethadione ("Tri-dione") in Treatment of Epilepsy. DR. HARRY L. KOZOL and DR. WILLIAM G. LENNOX.

Tetraethyl Lead Poisoning: Delirium-Tremens-Like Psychoses with Encephaloneuropathy. DR. LEO ALEXANDER.

This paper will be published in full elsewhere.

NORTHERN CALIFORNIA SOCIETY OF NEUROLOGY AND PSYCHIATRY

George Johnson, M.D., *President, in the Chair*

Regular Meeting, Dec. 5, 1946

Phenomena of Sensory Extinction. DR. NORMAN REIDER, San Francisco.

This paper was published in full in the June 1946 issue of the ARCHIVES, pages 583-590.

DISCUSSION

DR. CHARLES D. ARING, Cincinnati: It has been taught that the neurologic examination consists essentially in comparison of the form and functions of one

side of the body with those of the other, and of the functions of the patient with those of the examiner. It seems that to this definition it must now be added that simultaneous testing of the two sides may be necessary. The phenomenon of extinction or suppression requires further refinement of the local technic of neurologic examination. The point made by Dr. Reider that the manifestations of extinction will be missed unless double sensory testing is practiced is now obvious.

This factor in the sphere of vision was first called to my attention about twelve years ago by Dr. Gordon Holmes in the wards of the National Hospital, London, when he demonstrated what may now be termed suppression or extinction; then it was called visual inattention. It was thought to represent lack of attention or concentration, and possibly to be due to a lesion of the frontal lobe or, as I recall, to minute or early lesions in the neighborhood of the visual fibers. As has been reported by Dr. Reider, further studies have revealed that extinction may affect any sensation.

It is interesting that one cannot get some evidence in the matter with the electroencephalographic technic if, as Dr. Reider believes, the phenomenon is related to the extinction phenomenon of Dusser de Barenne. I do not believe that a tantalum plate in the skull would make any difference in this regard, since it has been shown that one may record quite satisfactorily through them. I wonder whether there is any relation between handedness and extinction?

I myself have increasingly been able to demonstrate extinction to the satisfaction of students and house officers in patients with cerebral lesions, an experience which I am sure will be universal when the technic of simultaneous or double sensory stimulation comes to be more generally used in the neurologic examination.

DR. MEYER A. ZELIGS, San Francisco: One might comment briefly on the nature of the causalgic phenomenon associated with irritation of homologous areas in the opposite extremity, which Dr. Reider described. I do not know whether or not Dr. Reider or Dr. Bender was able to demonstrate the phenomena of sensory extinction with disease of the spinal cord.

Livingston's theories (*Pain Mechanisms: A Physiological Interpretation of Causalgia and Its Related States*, New York, The Macmillan Company, 1943) are helpful in understanding irritation in homologous areas on the two sides of the body—why persons with causalgia, when faced with a noxious stimulus, not only have pain in the affected area but also may have it in the opposite extremity.

Livingston expressed the belief that in the causalgic state there is a constant bombardment of pain impulses coming in through sympathetic pathways at a spinal level, setting up an irritative state in the "internuncial pool" of neurons at that level. He stated the belief that the explanation of causalgia, and of causalgic phenomena in homologous areas, is this irritation of the internuncial pool, which extends both contralaterally and horizontally. Persistent noxious stimuli passing through this internuncial system produce a "reflex dystrophic state," which may cause a similar disturbance on the opposite side. I think such a neural mechanism probably represents an entirely different phenomenon from that which Dr. Reider has described, but it may be of value in helping to understand sensory extinction phenomena in the cortex.

DR. EPHRAIM ROSEMAN, Louisville, Ky.: Apparently, this extinction phenomenon, which I prefer to think of as a suppressor phenomenon, is an effect of stimulation. The examiner has to stimulate one side all the time. It would seem to me that this study is good clinical correlation of the work of Dusser de Barenne and McCulloch (Dusser de Barenne, J. G., and McCulloch, W. S.: *J. Neurophysiol.* 4:311, 1941. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.

ibid. 4:324, 1941) in monkeys and chimpanzees, in which they identified definite suppressor areas, e. g., areas 2S, 4S, 8S and 19S. By stimulation of these areas they obtained the suppressor phenomenon, and the electroencephalogram showed waves which decreased in amplitude, beginning closest to stimulated areas and then spreading. Sometimes it would take a few seconds for this wave of electrical suppression to spread; at other times, a little longer. Stimulation was either with strychnine or with electric current. These areas can be defined histologically as Bailey has shown. It seems that Dr. Reider's material may be correlated with experimental observations.

I should like to ask whether Dr. Reider knows of any case in which the suppressor phenomenon occurred without preexisting history of sensory loss or defect of the visual fields. Such an occurrence would be clinical evidence corroborating the work of Dusser de Barenne and McCulloch.

DR. NORMAN REIDER, San Francisco: I do not know the correlation between handedness and this phenomenon. It is true that most injuries have been on the right side of the brain in the cases reported to date. It would be immeasurably more difficult to demonstrate suppression in cases of damage to the left side of the brain because of speech deficit.

Dr. Zeligs has cited Livingston's theory of the spread of causalgic pain. The phenomenon that occurs with injury of the nerve root or the peripheral nerve is an intensification of sensation in the causalgic syndrome, rather than the obscuration of suppression or extinction. Bender has stated the belief that extinction and intensification belong in the same general category of behavior.

I made brief reference to Dr. Roseman's question when I said that I suspected strongly that if the phenomenon of obscuration is found it may be considered as evidence of prior, severer, damage than that which the patient shows at the time of examination. I have no evidence of the phenomenon having occurred without previous damage, but theoretically it should be possible.

Book Reviews

Fundamentals of Clinical Neurology. By H. Houston Merritt, M.D.; Fred A. Mettler, M.D., and Tracy Jackson Putnam, M.D. Price, \$6. Pp. 289, with 96 figures and 8 tables. Philadelphia: The Blakiston Company, 1947.

This volume is different from most works on neurology in that it is packed with anatomic facts, illustrated by many diagrams, but deficient in graphic clinical descriptions that make the subject come alive. The material would probably be better termed applied neuroanatomy. The descriptions are terse and require of the reader a considerable power of visualization of the nervous system in its three dimensional aspect. A great many anatomic minutiae are introduced, the majority of which are based on patient studies of the hodology of the nervous system, but which are not known to have anything in the way of clinical expression. This makes for hard reading and harder remembering. Neurology is a complex subject, but this work, in emphasizing the complexities, tends to make it almost discouraging, however far this may be from the authors' intention.

The first part is a brief discussion of the clinical means and physical diagnosis of neurology. Much of the detail of the history taking and physical examination, which is recorded in many texts and which the practitioner should already know, has purposely been left out. Burdensome and lengthy descriptions of variations of reflexes and occult signs—usually more confusing than edifying—have been avoided.

The second part, about five sixths of the text, is neuroanatomy as related to the syndromes one meets in the clinic. Treatment is mentioned only briefly. Systematically, each level of the peripheral and central nervous systems is treated. Diagrams, illustrations and charts are profuse and used well, making for easy and quick reference. The verbiage, moreover, is reduced. In general, controversial issues are avoided. The diagrams of the thalamic nuclei and their cortical connections (chapter 13), however, are included more for the benefit of the experienced neurologist than that of the practitioner, especially since specific localized function of the thalamus is not discussed. The chapter on the cerebrospinal fluid is well worth the space allotted to it. The clinical aspect of the autonomic nervous system has been almost completely neglected.

The value of this book lies in its emphasis on the deductive method of diagnosis—the anatomic basis of neurology. Surely, the practitioner cannot help but acquire a wholesome, scientific approach to neurologic problems from this text as a foundation. It would be worth while to dissect a brain as one reads the text.

CORRECTION

In the April 1947 issue of the *ARCHIVES* (57:481, 1947), the address of Drs. Wilder Penfield and William Feindel was given as Toronto, Ontario, Canada. Both authors are in Montreal, Canada.

ACTIVATED ELECTROENCEPHALOGRAPHY

I. CHARLES KAUFMAN, M.D.

BOSTON

CURTIS MARSHALL, M.D.

CHICAGO

AND

A. EARL WALKER, M.D.

BALTIMORE

With the Technical Assistance of

ELIZABETH M. BERESFORD, B.A., and GEORGE HOWE, B.S.

IN CASES of idiopathic epilepsy electroencephalographic abnormalities are commonly present, in the form of generalized dysrhythmias.¹ In a series of 240 cases of post-traumatic epilepsy these abnormalities were encountered in only 9.8 per cent, although foci of slow waves, probably due to the localized cerebral injury, were present in 77.7 per cent of the cases in which examination was made one to three years after injury.²

Accurate localization of the area of the cerebral cortex giving rise to the convulsive manifestation in post-traumatic epilepsy is necessary for surgical treatment of the condition. Since it seemed possible that an epileptogenic focus might be more susceptible to a convulsant drug than normal cerebral cortex, an attempt was made to activate the focus selectively by altering the chemistry of the blood. By using electroencephalographic recording to determine the activation before clinical manifestations appeared, it was hoped that the focus might be located without inducing a generalized seizure.

TECHNICS

The observations were made on a group of patients with post-traumatic epilepsy admitted to Cushing General Hospital for special study and on a small number of nonepileptic patients with cerebral wounds. The epileptic group consisted of patients who because of failure to respond to medical management were being considered for surgical therapy.

The work described in this paper was performed while the authors were assigned to Cushing General Hospital, Framingham, Mass.

1. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electroencephalogram in Diagnosis and in Localization of Epileptic Seizures, *Arch. Neurol. & Psychiat.* **36**:1225 (Dec.) 1936. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, *ibid.* **50**:111 (Aug.) 1943.

2. Walker, A. E.: Problems in Post-traumatic Epilepsy, read at the annual meeting of the American Psychiatric Association, Chicago, May 1945.

The electroencephalograms were made from electrodes placed conventionally on the scalp, with additional electrodes about the site of the healed wound or cranial defect and at least one electrode in a comparable position on the opposite side of the head. For "monopolar" recording an electrode attached to the ipsilateral ear was used as a common lead. The electroencephalograph was a four channel machine operating into an ink writer. In some cases two four channel machines were used simultaneously, the leads to the second machine being arranged for push-pull ("bipolar") recording from electrodes about the site of injury.

METHODS OF ACTIVATION

HYPERVENTILATION

It is well known that alterations of the acid-base equilibrium of the blood will increase or diminish the likelihood of convulsive seizures.³ The usual technic of hyperventilation induces electroencephalographic changes in 20 to 35 per cent of epileptic patients, but determination of the actual change in the carbon dioxide content and the p_H of the cortical cells is a difficult, if not impossible, feat. Measurement of the respiratory exchange was attempted but was found unsatisfactory, owing to the difficulty of having the patient overventilate at a given rate and depth. The technic as employed by Davis and Wallace⁴ was found to be too exacting for epileptic patients with neurologic disorders. In a group of 7 patients, all of whom seemed willing to cooperate, an attempt was made to obtain standard hyperventilation at a rate of 15 cycles per minute, each cycle representing an exchange of 20 cc. of air per pound of body weight. Kymographic recording of the respiratory exchange showed that individual patients achieved from 40 to 112 per cent of the standard. One patient (breathing 14.2 cc. of air per pound of body weight fifteen times a minute) had a jacksonian convulsion during the hyperventilation; the others did not have significant alterations in the electroencephalograms. Hyperventilation did not seem to be a consistent, satisfactory method for activating an epileptic focus.

HYDRATION

Hydration has been suggested as a technic for inducing convulsive phenomena in persons subject to epilepsy.⁵ While clinical convulsions may be induced with this method in 25 to 40 per cent of such persons, it is a difficult procedure to control quantitatively. To 1 patient 1,000

3. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Response to Overventilation and Its Relation to Age, *J. Pediat.* **23**:497, 1943. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electroencephalogram of Drugs and Conditions Which Influence Seizures, *Arch. Neurol. & Psychiat.* **36**:1236 (Dec.) 1936.

4. Davis, H., and Wallace, W. M.: Factors Affecting Changes Produced in Electroencephalogram by Standardized Hyperventilation, *Arch. Neurol. & Psychiat.* **47**:606 (April) 1942.

5. McQuarrie, I.: Epilepsy in Children: The Relationship of Water Balance to the Occurrence of Seizures, *Am. J. Dis. Child.* **38**:451 (Sept.) 1929.

cc. of isotonic solution of sodium chloride was given intravenously over a period of ninety minutes, without any change in the electroencephalogram. In a series of 8 patients, 4 of whom had post-traumatic epilepsy and 4 post-traumatic encephalopathy without seizures, the hydration test, as described by Penfield and Erickson,⁶ was carried out after anti-convulsant drugs had been withdrawn for a few days. The procedure is as follows: 1. Fluid is forced by mouth up to 3,000 to 6,000 cc. per day, an attempt being made to give equal amounts in each six hour period. 2. Pitressin, 0.5 cc., is injected intramuscularly every two hours during the procedure. 3. A diet containing considerable amounts of carbohydrate in various forms is given.

Under this regimen, all but 1 of the epileptic patients suffered such severe nausea and vomiting within twenty-four hours that the test had to be discontinued. Gains in weight of from 1.5 to 5.5 pounds (0.6 to 2.5 Kg.) were noted. No patient showed electroencephalographic changes, although 1 had a generalized seizure two hours after the test. In the group of nonconvulsive patients the gastrointestinal disturbances did not occur, but none of the patients had electroencephalographic alterations. It seemed inadvisable to use the procedure routinely, although it was obvious that the epileptic group reacted differently to the test than did the nonepileptic group.

ALCOHOL

Clinical experience has shown that seizures are prone to occur a day or two after an epileptic patient has indulged in alcoholic beverages.⁷ In view of this fact, electroencephalograms were made on a series of 16 patients, 12 of whom were epileptic, during, immediately after and at intervals up to seventy-two hours after the rapid intravenous administration (2 to 3 min.) of 40 to 150 cc. of 10 per cent alcohol. In 4 instances alcohol levels in the blood were found to range from 100 to 150 mg. per one hundred cubic centimeters. In the nonepileptic group no alterations were noted in the electroencephalograms. In the epileptic group the alpha rhythm became more prominent and the amplitude of the previous abnormal activity decreased. All patients showed clinical evidence of alcoholic intoxication, although none was unable to walk.

TRIMETHADIONE

It has been noted that some patients being treated with trimethadione ("tridione") for petit mal have exhibited grand mal attacks.⁸ For

6. Penfield, W., and Erickson, T. C.: *Epilepsy and Cerebral Localization*, Springfield, Ill., Charles C Thomas, Publisher, 1941.

7. Lennox, W. G.: *Alcohol and Epilepsy*, *Quart. J. Stud. on Alcohol* 2:1, 1941.

8. Lennox, W. G.: *The Petit Mal Epilepsies: Their Treatment with Tridione*, *J. A. M. A.* 129:1069 (Dec. 15) 1945.

this reason, 18 patients with post-traumatic epilepsy were given trimethadione intravenously in doses of 50 to 500 mg. on a total of twenty-six occasions. Of the 18 patients, 12 had been given 500 mg. intravenously on at least one occasion. In no instance was there any noticeable effect on the electroencephalogram, but 1 patient, approximately thirty minutes after receiving the drug and after the electroencephalographic recording had been completed, had a focal epileptic attack, which did not become generalized.

ELECTRIC SHOCK

Because electric shock has proved to be such a simple and relatively innocuous convulsant agent, it was used in a group of 11 patients with post-traumatic epilepsy. Seven patients were given 200 milliamperes for 0.05 to 0.15 second, using a 60 cycle sine wave current. They presented only a startle reaction or mild tonic spasm at the instant of application of the stimulus. Four patients received 2 to 5 milliamperes of square wave, pulsating direct current for two to three seconds and felt only a sensation of warmth. The electroencephalograph was turned off just before the shock and on again immediately afterward. In no instance was there significant alteration in the electroencephalogram five seconds after the stimulus.

PENICILLIN

In view of the fact that penicillin has been shown to have a convulsant effect when applied to the cerebral cortex,⁹ 100,000 units of the drug was given intravenously to a series of 5 patients, 4 of whom had organic disease of the brain, and the electroencephalographic record followed for thirty-five to fifty minutes. In no instance was any change noted in the record.

SODIUM CYANIDE

Because the cytochrome oxidase system¹⁰ is impaired in patients with advanced dementia paralytica, in whom convulsive manifestations are common, and because cyanide is a specific poison for these enzymes, it was thought advisable to determine the effect of cyanide¹¹ on the patient with post-traumatic epilepsy. In a series of 17 patients, 14 of whom had seizures, a 2 per cent solution of sodium cyanide was administered intravenously. Three patients were given 0.3 mg. and the rest

9. Walker, A. E., and Johnson, H. C.: *Penicillin in Neurology*, Springfield, Ill., Charles C Thomas, Publisher, 1946.

10. Hadidian, Z., and Hoagland, H.: *Chemical Pacemakers: I. Catalytic Brain Iron; II. Activation Energies of Chemical Pacemakers*, *J. Gen. Physiol.* **23**:81, 1939.

11. Rubin, M. A., and Freeman, H.: *The Influence of Cyanide on Brain Potentials in Man*, *J. Neurophysiol.* **1**:527, 1938.

0.4 mg., per kilogram of body weight. Of the first group, 1 patient had no clinical or electroencephalographic reaction. In all the other patients a respiratory gasp occurred eight to twenty seconds after the injection, and a progressive slowing of the predominant activity appeared in their electroencephalograms (fig. 1). For example, in 1 patient the gasp occurred twenty seconds after the injection into the antecubital vein. Five seconds later the predominant rhythm in all leads was 8 cycles per second; five seconds later, 6 cycles per second, and eight seconds later, 2 cycles per second. Fifty seconds after the injection, widespread muscular twitching occurred throughout the body. Within seventy seconds after inhalation of 2 ampules (0.4 cc. each) of amyl

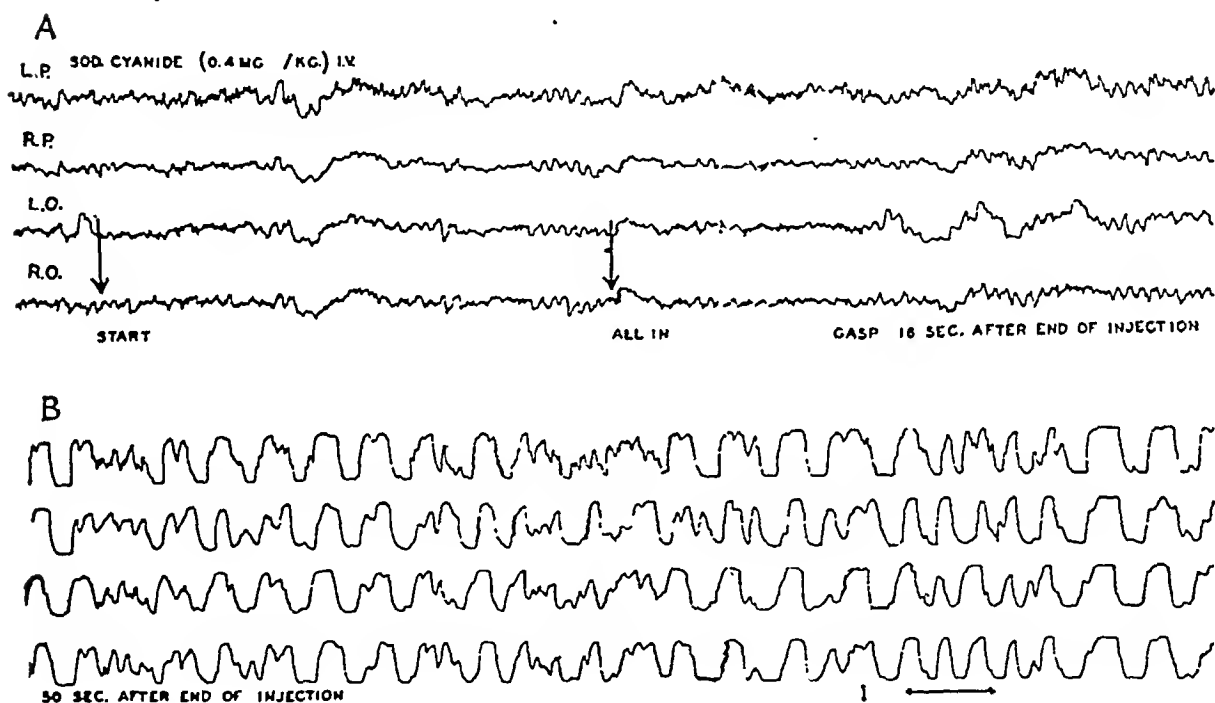


Fig. 1.—Records showing the effect on the electroencephalogram of sodium cyanide (0.4 mg. per kilogram of body weight) given intravenously. *A* is the control record, taken at beginning of the injection; *B*, the record taken fifty seconds after the injection, showing the generalized slow high voltage waves. *L.P.* indicates leads from the left parietal region and the left ear; *R.P.*, leads from the right parietal region and the right ear; *L.O.*, leads from the left occipital region and the left ear; *R.O.*, leads from the right occipital region and the right ear.

The vertical line at the base indicates a calibration of 50 microvolts; the horizontal line, an interval of one second.

nitrite, the slow waves had disappeared from the electroencephalogram. The slow waves were unrelated to the site of injury or to the site of electroencephalographic abnormality. In some cases the head and eyes turned to one side without constant relation to the site of injury. Occasionally opisthotonos developed. The reaction to the cyanide was the same in the nonepileptic as in the epileptic group.

ACETYLCHOLINE

It has been suggested that acetylcholine may be related to epileptic states.¹² A series of 18 patients, 15 of whom were epileptic, were given 100 to 300 mg. of acetylcholine chloride in aqueous solution at rates of injection varying from 20 to 60 mg. per minute. No change in the electroencephalogram was noted in any patient except for a decrease in amplitude of the waves for two minutes after the injection in 1 instance. The patients experienced a feeling of warmth and occasionally coughed, but had no other clinical manifestation related to the injection.

METRAZOL

It has been known for some time that clinical seizures could be induced in patients subject to epileptic attacks with a smaller dose of metrazol than that needed to convulse normal persons.¹³ Lennox suggested that small amounts of metrazol might induce electroencephalographic alterations without precipitating a clinical attack. We found that the intravenous administration of 1 cc. of a 10 per cent solution (100 mg.) of the drug induced no clinical or electroencephalographic manifestations. Nor was the intravenous injection of 1.5 cc. of the metrazol solution more effective, but 2 cc. induced abnormalities in the electroencephalogram in a certain percentage of subjects. The technic was then standardized.

Metrazol, usually 2 cc. of a 10 per cent solution (200 mg.), was injected as rapidly as possible into the antecubital vein while an electroencephalogram was being recorded. The needle was left in place, and as soon as alterations were seen in the tracing, usually within thirty to sixty seconds, a solution of phenobarbital sodium (0.26 Gm.) was administered intravenously in an attempt to prevent the development of clinical convulsions. In a group of patients the metrazol was given by intramuscular administration, 6 mg. per kilogram of body weight being injected into the deltoid muscle. Phenobarbital sodium was given intravenously or intramuscularly as soon as changes were seen in the electroencephalogram, usually three to four minutes after the metrazol had been given.

12. Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on Electrical Activity of the Cortex, *Arch. Neurol. & Psychiat.* **48**:382 (Sept.) 1942. Williams, D., and Sweet, W. H.: Effect of Choline-Like Substances on Cerebral Electrical Discharges in Epilepsy, *J. Neurol. & Psychiat.* **4**:32, 1941. Forster, M., and McCarter, R. H.: Changes in Electrical Activity of the Cortex Due to Application of Acetylcholine, *ibid.* **54**:71 (July) 1945.

13. Langelüddeke, A.: Die diagnostische Bedeutung experimentell erzeugter Krämpfe, *Deutsche med. Wchnschr.* **62**:1588, 1936. Schönmehl: Provokation von epileptischen Krampfanfällen, *Versuche und Ausblick*, München. *med. Wchnschr.* **83**:721, 1936.

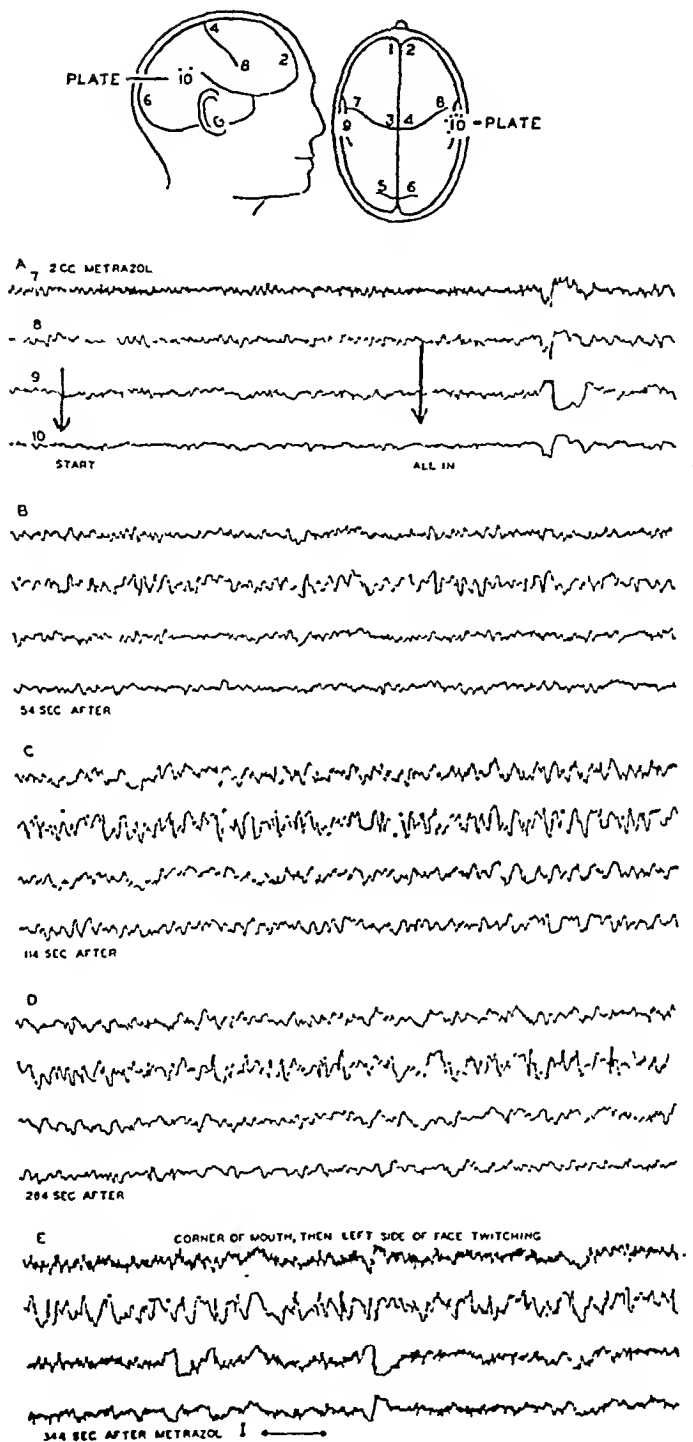


Fig. 2.—Electroencephalograms of a patient with post-traumatic epilepsy, showing activation of a focus by 2 cc. of a 10 per cent solution of metrazol given intravenously (A). Fifty-four seconds after the injection, high voltage 5 per second waves appeared in the tracing from the right inferior central region, whereas the activity in the other areas was little changed (B). Approximately two minutes after the injection all leads showed increased high amplitude activity, most pronounced in the left inferior central region (C). The general cortical activity became more irregular (D). Three hundred and forty-four seconds after the injection the spiky activity from the left inferior central region was more pronounced and twitching appeared (E).

The vertical line at the base indicates a calibration of 50 microvolts; the horizontal line, an interval of one second.

The results of activation with metrazol may be divided into electroencephalographic and clinical manifestations.

Electroencephalographic Changes.—Although in most instances slight alterations were present in the electroencephalograms from all parts of the head, in the majority of patients the changes were predominantly

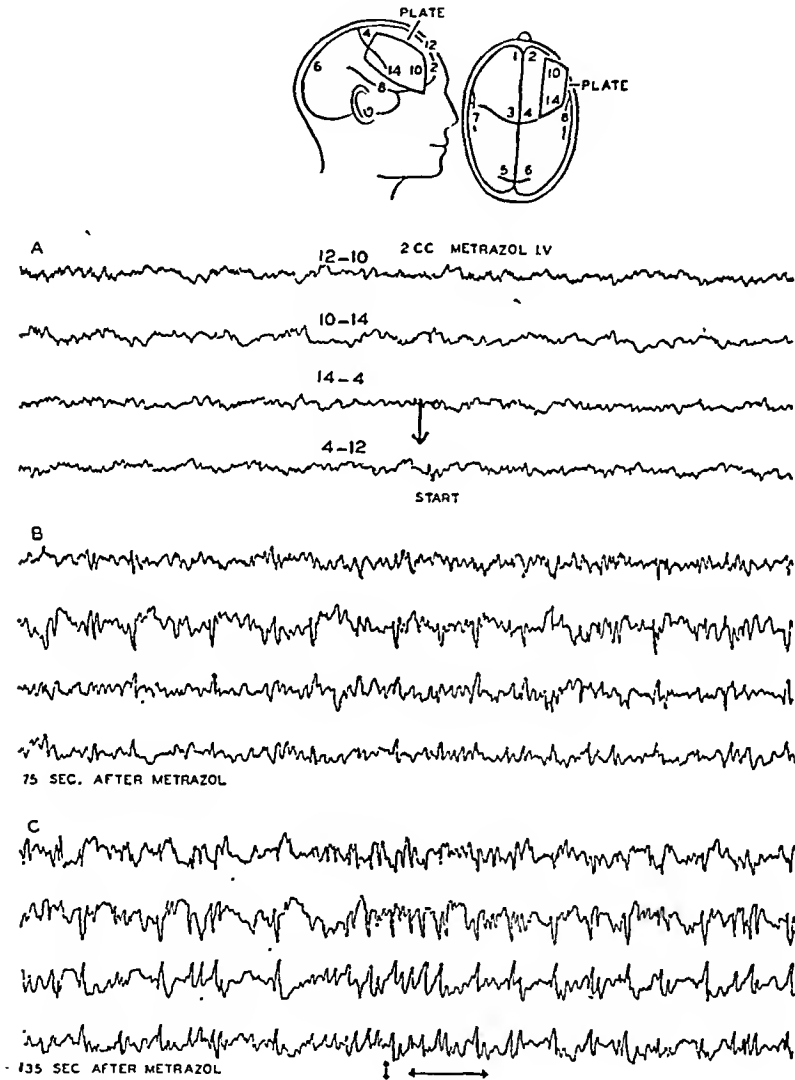
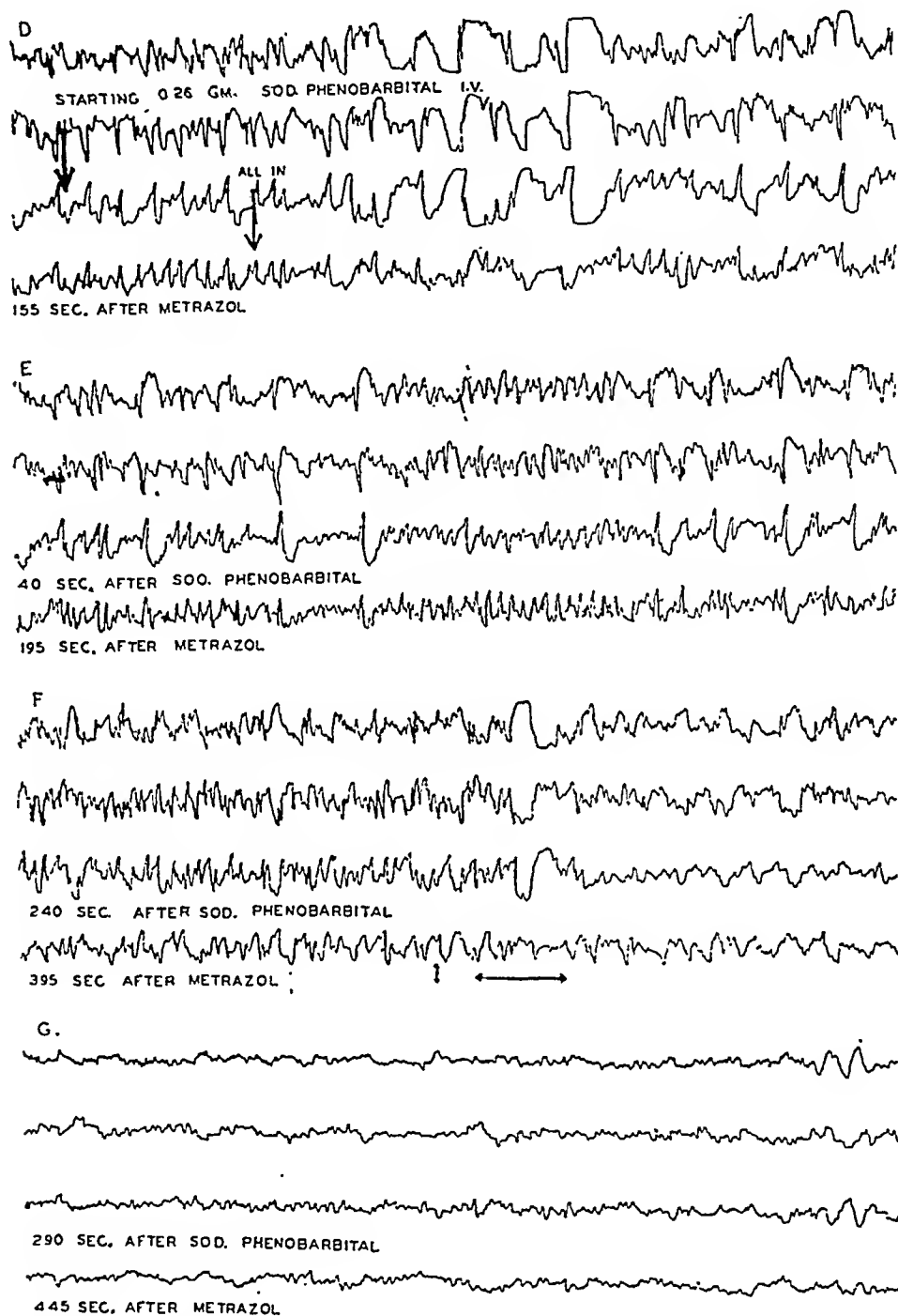


Fig. 3.—Electroencephalograms taken during activation with metrazol in a patient with post-traumatic epilepsy. The electrodes were placed on the scalp about a plate in the right frontal region, and the leads were arranged for push-pull recording.

(A) The record was taken during the intravenous administration of 2 cc. of a 10 per cent solution of metrazol (200 mg.); (B) seventy-five seconds after injection, spiking was seen in all records, but was most pronounced and out of phase in the tracings from electrode 14; (C) one hundred and thirty-five seconds after the administration of metrazol, the spikes were of greater amplitude.

or solely in the tracings from one region (fig. 2). Such alterations are referred to as localized electroencephalographic alterations and might

take the form of slow waves or humps having a frequency less than the alpha rhythm, or of spikes, either single or multiple (fig. 3), at times occurring rhythmically, giving the pattern a localized electroencephalo-



(D) One hundred and fifty-five seconds after the injection, the spiky activity was still pronounced. Intravenous administration of phenobarbital sodium (0.27 Gm.) decreased the amplitude of the abnormal activity, as shown in the succeeding records, taken forty seconds (E), two hundred and forty seconds (F) and two hundred and ninety seconds (G) after the administration of the anticonvulsant drug. On the basis of this activated electroencephalogram, the abnormal focus was considered to lie beneath point 14.

The short vertical sign at the base represents a calibration of the electroencephalograph for 50 microvolts; the horizontal line, an interval of one second.

graphic seizure (figs. 4 and 5).. These abnormalities, if present before activation, were usually aggravated by the metrazol. Such localized electroencephalographic alterations occurred in 60 per cent of the 97 patients tested.

In a smaller number of patients (10 per cent) generalized electroencephalographic alterations consisting of single or multiple slow waves or spikes were present simultaneously in tracings made from several

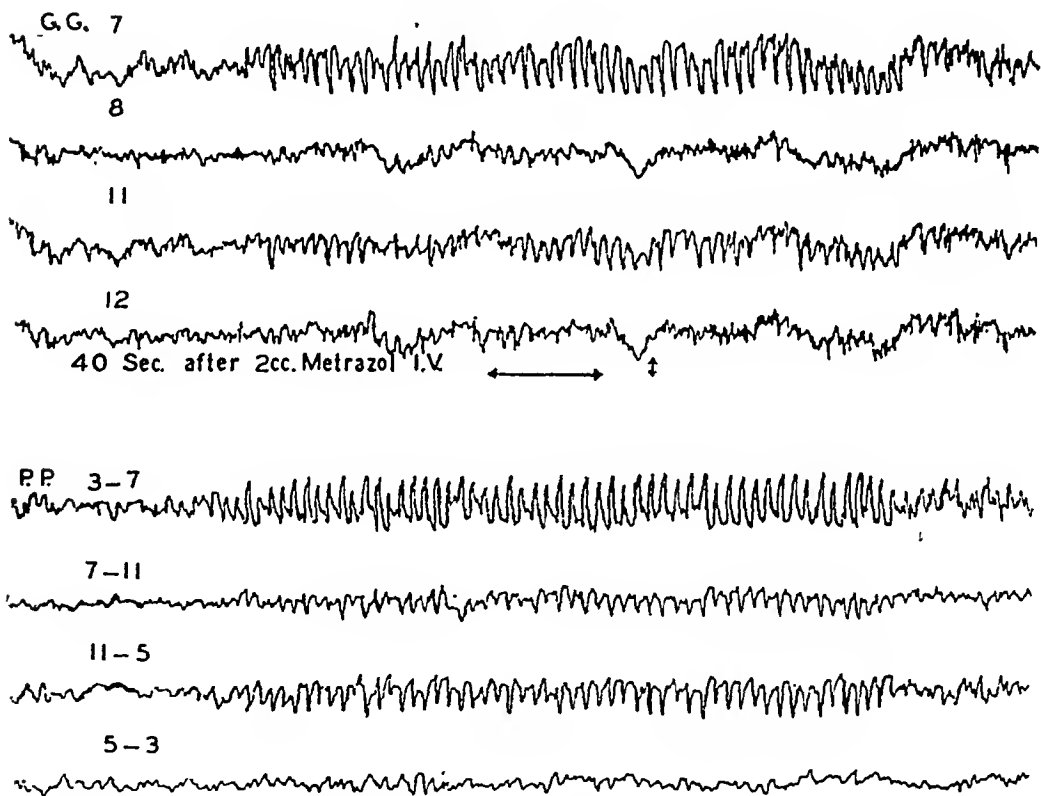
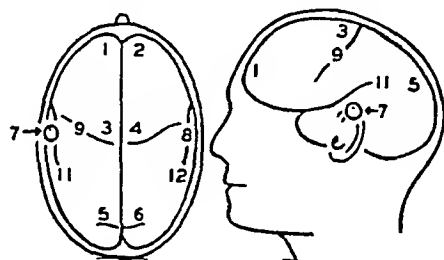


Fig. 4.—Electroencephalograms showing a predominant localized electroencephalographic seizure following the intravenous injection of 2 cc. of a 10 per cent solution of metrazol in a patient with post-traumatic epilepsy due to a penetrating wound in the left temporal region. All eight tracings are simultaneous recordings; the upper four being “monopolar” electroencephalograms from comparable areas of the two sides of the head and the lower four being push-pull recordings from about the cranial defect. The focus lies under point 7, the spiky waves having a higher amplitude and the push-pull recording showing out-of-phase activity from that region.

The vertical arrow under the first four tracings indicates a calibration of 50 microvolts; the horizontal arrow, an interval of one second.

parts of both sides of the head. In some instances the waves and spikes occurred rhythmically and simultaneously in all parts of the head from which recordings were taken, giving the pattern of a generalized electroencephalographic seizure (fig. 6).

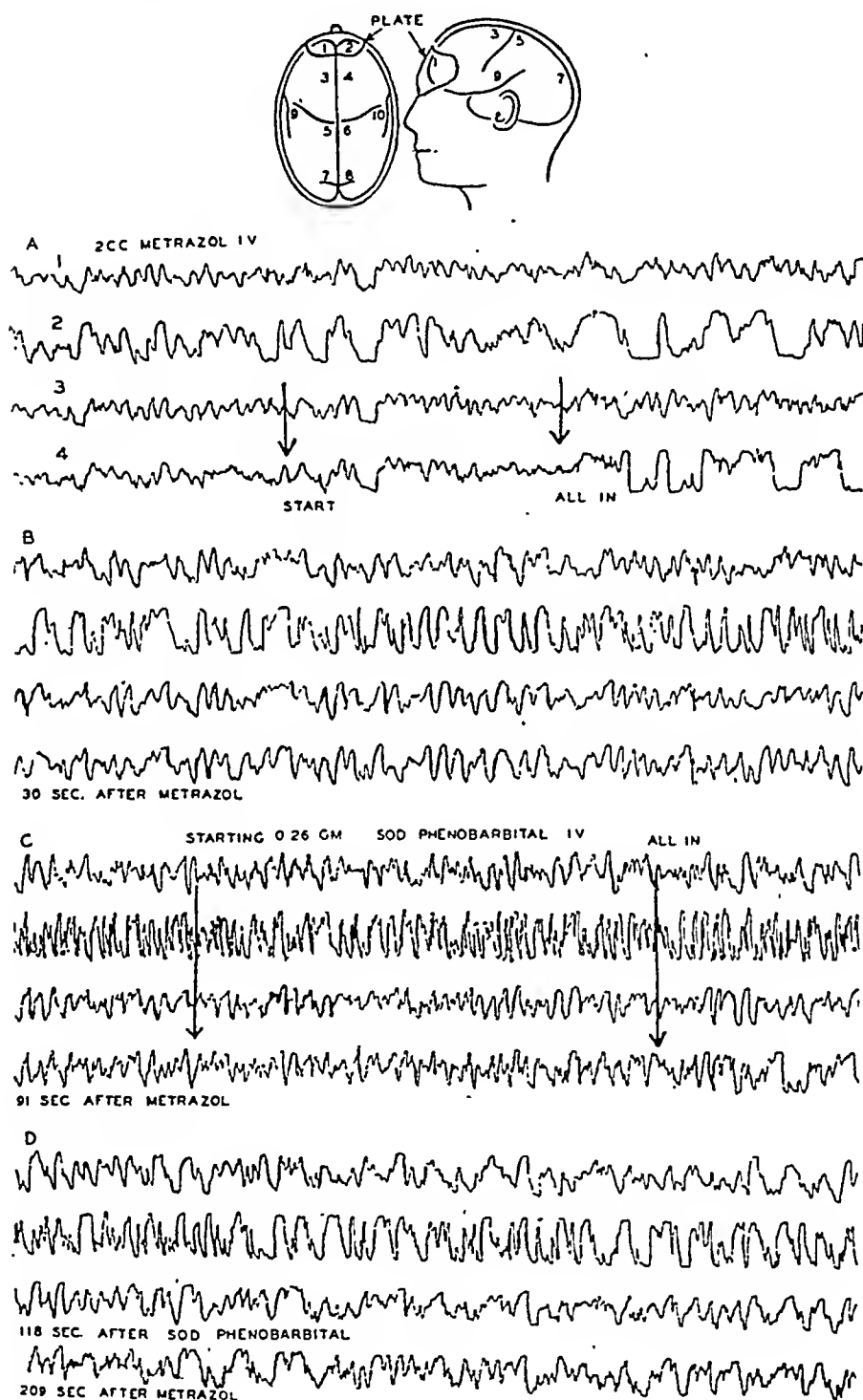


Fig. 5.—Activated electroencephalograms from a patient with post-traumatic epilepsy. A generalized slowing of the predominant rhythm occurred within thirty seconds after the injection of 2 cc. of a 10 per cent solution of metrazol, being most prominent in the second lead (A and B). Within a minute and a half of the injection the activity became faster and the waves sharper (C). The intravenous injection of 0.26 Gm. of phenobarbital sodium decreased the spiky fast activity (D).

Clinical Manifestations.—A small percentage of patients experienced sensory or motor phenomena such as they usually associated with their spontaneous seizures. In approximately one-half these patients the attack remained confined to one portion of the body and is referred to as a focal convulsion. In the remainder the attack began as or developed into a generalized seizure involving all parts of the body and being associated with loss of consciousness (table 1).

The seizures induced by metrazol had the characteristics of the patient's ordinary attacks. The fit was ushered in by the same aura, progressed in the usual order and had identical motor phenomena. The severity of the seizure was comparable to that of the spontaneous con-

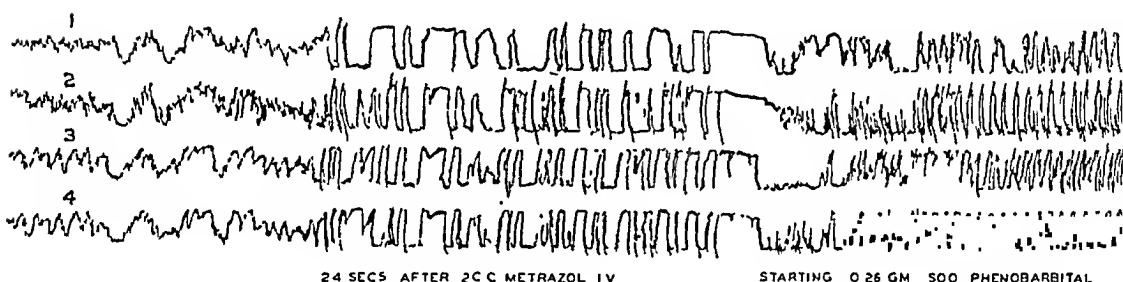
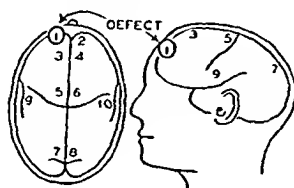


Fig. 6.—Electroencephalogram showing a generalized electroencephalographic seizure beginning practically simultaneously from the two frontal regions of the head after the intravenous injection of 2 cc. of a 10 per cent solution of metrazol in a patient with post-traumatic epilepsy. The leads are taken from the frontal region, as indicated, with the second electrode on the ear.

TABLE 1.—Results of Metrazol Activation in Patients with Post-Traumatic Epilepsy

	Number of Patients
Number of patients receiving metrazol activation *.....	97
Generalized electroencephalographic alterations.....	7
Localized electroencephalographic alterations.....	58
Localized and generalized electroencephalographic alterations....	10
Localized slow waves.....	83
Localized spikes.....	31
Localized electroencephalographic seizure.....	18
Generalized slow waves.....	5
Generalized spikes.....	6
Generalized electroencephalographic seizure.....	6
Clinical focal convulsion.....	10
Clinical generalized convulsion.....	14

* In a number of patients activation with metrazol was carried out more than once (table 4), but in this table a positive result in any category is included only once for each patient, although he may have had a positive result on each of four tests. Accordingly, the figures are smaller for each phenomenon in this table than in table 4.

TABLE 2.—Frequency and Number of Spontaneous Seizures and Incidence of
Convulsions Induced by Activation with Metrazol

	Number of Patients	Mean Weight of Patients, Lb.	Mean Number of Attacks	Mean Interval Between Attacks, Months	Mean Time Between Last Attack and EEG Examination, Months
Clinical convulsions...	19	162.2	5.7	2.0	2.4
No convulsions.....	19	152.1	9.7	0.9	1.8

TABLE 3.—*Results of Repeated Activation with Metrazol in Patients Without Primary Localizing Electroencephalographic Phenomena*

	Electroencephalographic Alterations						
First test.....	None 43			Generalized 10			Localized 44
Second test.....	Generalized 1	None 21	Localized 8	None 1	Generalized 2	Localized 3	
Third test.....	Generalized 0	None 5	Localized 0	None 1	Generalized 0	Localized 1	
Fourth test.....		None 2					
Fifth test.....		None 2					

TABLE 4.—*Results of Repeated Activation with Metrazol**

	Test No.											Total
	1			2			3		4		5	
	On†	Off†		On	Off		On	Off	On	Off	Off	
	IV	IV	IM	IV	IV	IM	IV	IV	IV	IV	IV	
Generalized electroencephalographic alteration.....	2	8	0	1	4	0	0	1	0	0	0	16
Localized electroencephalographic alteration.....	10	33	1	3	17	5	2	4	0	3	2	80
No electroencephalographic alteration...	9	30	4	9	25	3	3	6	1	1	3	94
Total.....	21	71	5	13	46	8	5	11	1	4	5	190
Generalized slow waves.....	2	1	0	0	2	0	0	0	..	0	0	5
Generalized spikes.....	1	4	0	0	0	0	0	1	..	0	0	6
Generalized electroencephalographic seizures.....	0	5	0	1	2	0	0	0	..	0	0	8
Localized slow waves.....	9	14	0	2	7	1	2	1	..	1	1	38
Localized spikes.....	3	13	1	2	7	4	1	2	..	3	2	38
Localized electroencephalographic seizures.....	1	11	0	1	6	1	0	1	..	0	0	21
Total.....	16	48	1	6	24	6	3	5	..	4	3	116
Clinical Phenomena												
Focal convulsions.....	0	5	0	0	4	0	0	1	0	0	0	10
Generalized convulsions.....	0	9	0	0	4	2	0	1	0	0	0	16

* IV means intravenous, IM intramuscular, administration.

† On indicates that the patient was receiving anticonvulsant medication at the time of the test; Off, that no medication had been received for at least three days prior to the examination.

vulsion. However, there was no relation between the frequency and number of attacks which the patient had had and their occurrence on activation with metrazol (table 2).

Repeated Activation with Metrazol.—Because a single activation with metrazol gave positive localizing electroencephalographic changes in less than one-half the patients studied, reexaminations were made on a number of patients showing no such alterations in the primary examination (tables 3 and 4). Approximataely one-third this group had localized electroencephalographic alterations on the second test. Reexamination was made also of a number of patients who had focal electroencephalographic alterations on the first test. Although the majority again had focal abnormalities, some showed no electroencephalographic alterations on the second activation. It must be concluded, then, that focal activation is not consistently found in the same patient on repeated examinations. However, when activated, the focus appears to be at the same locus. It would, then, seem worth while to reexamine by metrazol activation patients who do not show a focus on the first examination.

Activation by Intravenous and Intramuscular Injection of Metrazol.—To a group of 11 patients, 6 mg. of metrazol per kilogram of body weight was administered intramuscularly. Only 1 patient had a clinical generalized seizure, and only 2 showed localizing electroencephalographic changes (fig. 7). Nine of the 11 patients were given 2 cc. of a 10 per cent solution of metrazol intravenously, and all showed focal electroencephalographic alterations. It would seem, then, that while the intramuscular method of administration of metrazol may be less likely to produce clinical seizures, it is much less efficient in activating an epileptogenic focus.

Effect of Anticonvulsant Medication on Activation with Metrazol.—Routinely, patients were given no anticonvulsant medicament for three days before activated electroencephalographic recording. However, in a group of patients, activation with metrazol was carried out without preliminary elimination of drug therapy. In a series of 40 patients receiving such activations, 3 (7.5 per cent) showed generalized electroencephalographic changes and 15 (37.5 per cent) localized alterations. This is a definitely lower incidence of activation than that in the group not receiving anticonvulsant medication. However, none of the patients in this group had clinical convulsions. It may prove advisable to carry out activation with metrazol while the patient is receiving anticonvulsant medication in order to lessen the risk of inducing an overt convulsion.

Activation with Metrazol as a Prognostic Guide.—As a patient's attacks became controlled by medication, it was hypothesized that tolerance to metrazol, as determined by electroencephalographic and clinical

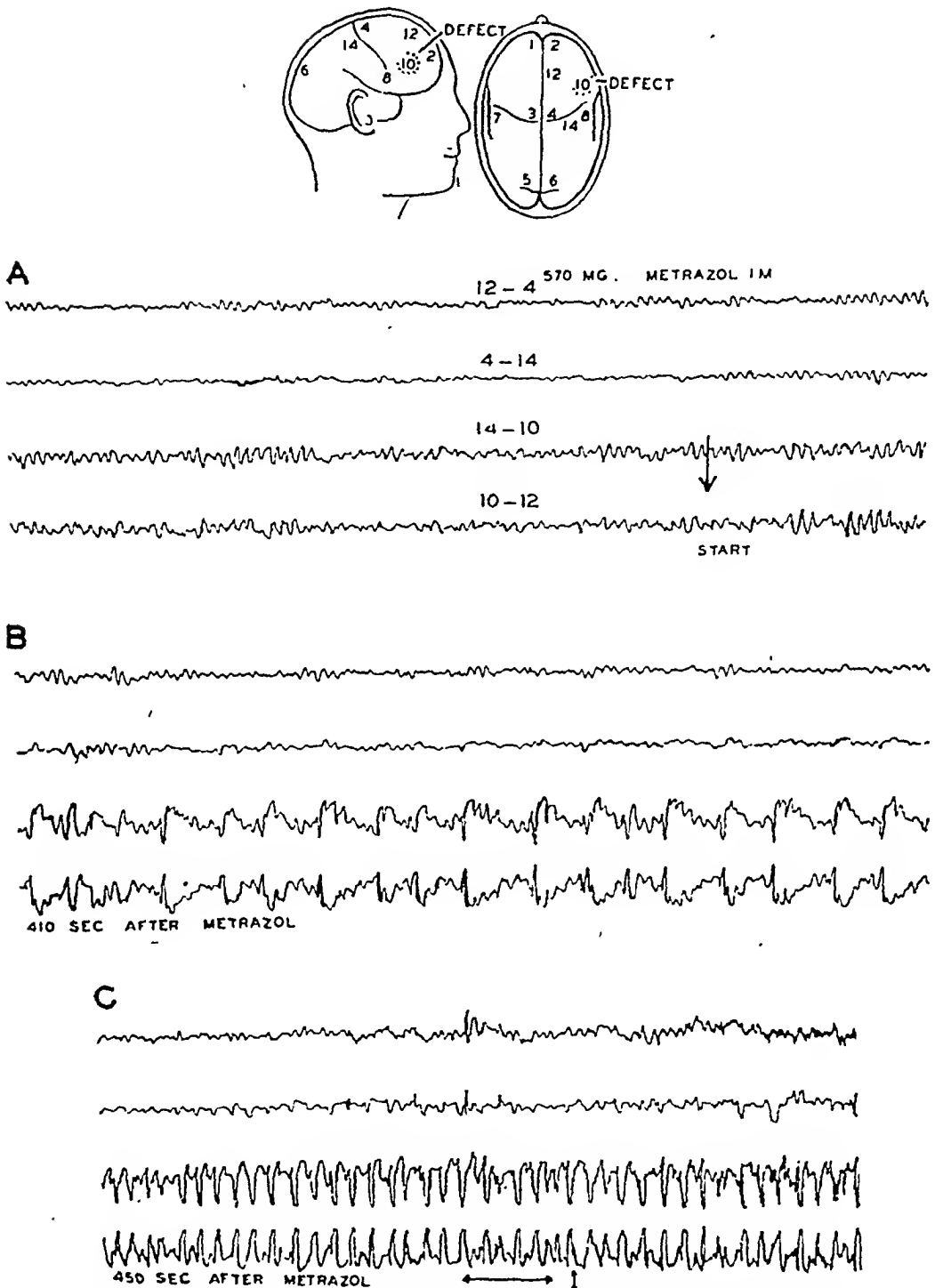


Fig. 7.—Electroencephalograms showing push-pull recording about the cranial defect of a patient with post-traumatic epilepsy (*A*). At the arrow, 570 mg. of metrazol was injected into the right deltoid muscle. Seven minutes later the cortical activity, as recorded by electrodes over and above the defect, showed rhythmic spikes (1 to 2 cycles per second), being out of phase in electrode 10 (*B*). Seven and one-half minutes after the injection the spikes had a 5 per second frequency and at times had small humps or domes between them, resembling to some extent the hump and spike pattern of petit mal (*C*). Even when the activity was very prominent in the tracing from the electrodes near the defect, the electroencephalogram from the electrodes in the paracentral region showed only slight alterations.

The vertical line at the base of the tracings represents a calibration of 50 microvolts; the horizontal line, an interval of one second.

responses to activation, might be increased. However, this did not appear to be the case, for patients who had had no attacks for six months had both electroencephalographic and clinical abnormalities on activation with metrazol, whereas some patients having attacks every two to three weeks showed no electroencephalographic or clinical reaction (table 2). The activation cannot, then, be considered an accurate prognostic or therapeutic guide.

Correlation of Electroencephalographic Foci and Epileptogenic Foci Observed at Operation.—In 39 of the patients the cerebral cortex was explored because of the uncontrollable epilepsy. At the time of cortical exploration either metrazol or electrical activation or both were carried out. In all instances in which a focus was demonstrated by the activated electroencephalographic method the locus of the focus was confirmed at the time of operation. Several technics were employed to remove the foci, with or without the scar. While the results of operation have been satisfactory so far, it is too soon to make a definite statement regarding the results of the procedure.

COMMENT

The value of actually witnessing the typical attack of an epileptic patient has been recognized for many years. But only recently have methods for inducing such attacks been seriously considered. In general, the technics of hyperventilation and hydration have not been very successful, either because of the low incidence of induced attacks or because of the unpredictable time of occurrence. The attack, when produced, however, has been typical of the patient's usual seizure. The use of metrazol to produce convulsions, suggested first by von Meduna,¹⁴ has the distinct advantage that the attack may be produced at the time the patient is under observation. Penfield and Erickson⁶ stated that the test is of doubtful value in cases of epilepsy, since it leads to seizures in a high percentage of nonepileptic as well as epileptic patients. This disadvantage is not serious if one is using the test to determine the pattern of the seizure in patients known to have convulsions. Penfield and Erickson admitted that the test "would be useful only if it is shown that small doses faithfully reproduce the patient's spontaneous attacks."¹⁵ This similarity we, as well as others, have demonstrated, although we have no doubt that if too large doses are given the pattern of a focal attack may be obscured by the rapid onset of a generalized attack.

14. von Meduna, L.: Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenia: I. Campher- und Cardiozol Krämpfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:235, 1935.

15. Penfield and Erickson,⁶ p. 458.

Perhaps the slow intravenous injection of a more dilute solution¹⁶ might be advisable in such circumstances.

By recording an electroencephalogram during the actual injection of the convulsant drug, the likelihood of a generalized seizure is decreased, since as soon as abnormalities become apparent an anticonvulsant drug may be given intravenously. We believe that the clinical and electroencephalographic information gained more than compensates for the possible risk of inducing a convulsive seizure.

SUMMARY

In a series of 97 patients with post-traumatic epilepsy, an attempt was made to activate the epileptogenic focus by hyperventilation, hydration, electric shock, intravenous administration of alcohol, and injection of trimethadione, penicillin, acetylcholine chloride, sodium cyanide and metrazol.

Of these methods, the injection of metrazol proved to give satisfactory focal activation in approximately 44 per cent of the patients on the first test and in a much higher percentage on repeated testing.

Intravenous administration was more effective than intramuscular injections.

Clinical seizures occurred in approximately 14 per cent of patients, but not if anticonvulsant medication was given before the test.

The electroencephalographic alterations induced with metrazol included focal slow waves, spikes or, somewhat less frequently, the rhythmic discharge of a seizure. The same alterations were less commonly recorded from all parts of the head.

Activated electroencephalography appears to be a useful diagnostic aid in the understanding of the mechanisms involved in post-traumatic epilepsy.

80 East Concord Street, Boston.

950 East Fifty-Ninth Street, Chicago.

16. Dr. E. Ziskind, of Los Angeles, in discussing a paper by one of us (A. E. W.)² presented at the one hundred and second annual meeting of the American Psychiatric Association in May 1946, stated that he was using that technic to determine convulsive thresholds and that it rarely precipitated a generalized convulsion.

FATAL CRYPTOGENIC NEUROPATHY

SAMUEL BROCK, M.D.

AND

CHARLES DAVISON, M.D.

NEW YORK

UNDER THE caption of "fatal cryptogenic neuropathy," we wish to put on record the clinical and pathologic observations in 3 cases in which the brunt of the disease was sustained by the peripheral nervous system (roots and nerves), though in 2 of the cases there were evidences of lesser involvement of other parts of the neuraxis. Use of the usual prefixes indicative of such higher involvement, to which the suffix "pathy" must needs be added, would lead to a compound and cumbersome title which would not emphasize the major implication of the peripheral nerves. However, we would not give the impression that we are describing a new disease, clinically or pathologically.

In the recent neurologic literature there are many well known references to special forms of neuritis or neuropathy the cause of which is unsettled. Thus, one may refer to the group of cases described by Guillain, Barré and Strohl in 1916,¹ and again by Guillain in 1936,² as well as to cases of acute febrile polyneuritis,³ certain instances of acute febrile polyneuritis with facial diplegia⁴ and a variety of other forms,⁵ such as relapsing or recurrent polyneuritis and polyneuritis associated with hematorporphyrinuria. In connection with the "radiculoneuritis with acellular hyperalbuminosis of the cerebrospinal fluid" which he

Presented at a meeting of the New York Neurological Society, March 4, 1947.

From the Neuropathological Laboratory and the Neuropsychiatric Service of the Montefiore Hospital for Chronic Diseases, and the Neurological Department of Columbia University College of Physicians and Surgeons.

1. Guillain, G.; Barré, J. A., and Strohl, A.: *Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire: Remarque sur les caractères et graphiques des réflexes tendineux*, Bull. et mém. Soc. méd. d'hôp. de Paris **40**:1462, 1916.

2. Guillain, G.: *Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid*, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936.

3. Holmes, G.: *Acute Febrile Polyneuritis*, Brit. M. J. **2**:37, 1917.

4. Bradford, J. R.; Bashford, E. F., and Wilson, J. A.: *Acute Infective Polyneuritis*, Quart. J. Med. **12**:88, 1918. Forster, F. M.; Brown, M., and Merritt, H. H.: *Polyneuritis with Facial Diplegia*, New England J. Med. **225**:51, 1941.

5. Wilson, S. A. K.: *Neurology*, Baltimore, Williams & Wilkins Company, 1940, vol. 1.

described, Guillain² stressed the cytoalbuminous dissociation and the favorable prognosis. He expressed the belief that the disease is of infectious origin, i. e., due to a neurotropic virus. Guillain² described the onset of the disease—sometimes abrupt—the progressive areflexic flaccid paralysis, the mild to moderate muscular wasting, the slight objective sensory defects, the neuritic pains in the limbs and the occasional involvement of the cranial nerves. Despite the fact that over thirty years have passed since the French called attention to the clinical picture, the cause of the disease has escaped detection.

In reporting the following 3 fatal cases, in 2 of which there were repeated evidences of increased protein in the spinal fluid, we would stress the fact that our cases of fatal "neuritis or neuropathy" were characterized by considerable variation in duration and symptoms. Despite a similarity in neuropathologic changes, it is not at all certain that we are dealing with a disease due to a single cause.

REPORT OF CASES

CASE 1.—E. W., a single woman aged 26, a stenographer, entered the Neurological Institute of New York on May 26, 1936 and was discharged to the Montefiore Hospital on Nov. 16, 1936. She died on Jan. 7, 1937.

She had a past history of measles and scarlet fever and of acute nephritis following a "cold" in 1932; the last disease was associated with edema of the ankles and the eyelids.

The patient's sister, M. W., aged 22, born of the union of the patient's father and her mother's sister, was admitted to the Neurological Institute of New York on Aug. 9, 1935. She complained of progressive loss of vision, occasional dizzy spells, tingling sensations, slight numbness and stiffness of the fingers of the right hand and diplopia of two weeks' duration. The right pupil was slightly larger than the left; both reacted sluggishly to light; there were slight photophobia and generalized hyperreflexia. Ophthalmologic examination disclosed pallor of the temporal side of the left fundus. Examination of the spinal fluid disclosed 7 cells per cubic millimeter, a negative reaction for globulin, 24 mg. of protein per hundred cubic centimeters, a colloidal gold curve of 112211100 and a negative Wassermann reaction; the blood also gave a negative Wassermann reaction. The diagnosis was multiple sclerosis with retrobulbar neuritis.

E. W. became ill in March 1936. She noticed that her arms became unusually tired and her fingers stiff when typing. On April 13 her lower limbs seemed to drag because of weakness. Soon both lower limbs became weaker, the left being affected more than the right. On April 23 the right arm became weak. On April 28 the left arm was similarly affected. She could no longer walk. In typing she could use only either index finger.

She was admitted to the Neurological Institute on May 26, 1936. In June of the same year she became unable to feed herself. Toward the middle of that month she was able to move only one finger at a time. There was no history of fever, pain, headache, deafness, tinnitus or disturbance in vision. By June 8 the flaccid paralysis in the four limbs had become extreme and continued with little or no change over the subsequent months. Only the faintest flicker of movement at the left elbow (left biceps muscle) and slight movement of the left index finger were observed. The muscles of the neck, chest and abdomen seemed

relatively uninvolved. The innervations of the cranial nerves were normal. Sphincter action was unaffected. Muscular atrophy was noted in the interossei and in the anterior and posterior tibial groups in July 1936. Later in July there was diminished power in holding the head forward against resistance. No sensory defects were noted until late July, when vibratory sense was found to be diminished over the right tibia. The sensory defect disappeared in the next few months. In late July of 1936 blurring of the upper margins of the optic disks first appeared; this change in the disks progressed little, if any. In September 1936 striate hemorrhages were found above the papillae and the retinal vessels seemed more engorged. All the deep reflexes were missing except for an occasional response in the left pectoral and biceps muscles.

Because of the presence of infected tonsils, a tonsillectomy was performed on October 14.

On Nov. 5, 1936, the physical status was as follows: There were pallor of the nails, coldness of the extremities, slight cervical kyphosis and some tenderness and limitation of passive movement of the joints of the limbs, especially the elbows. Muscular atrophy was extreme in the lower extremities and slight in the upper extremities. She was able to use the muscles of the neck and the upper thoracic and lower lumbar regions, particularly on the left side; there were increased irritability and tenderness of the muscles of the upper extremities. Flaccid paralysis of all muscles of the limbs was noted; the scapular and the left pectoral and biceps muscles were paretic. There was generalized areflexia except for occasional responses in the left pectoral and biceps muscles. No gross sensory defects were noted. There were some blurring of the margins of the disks and slight evidence of old retinitis. The visual fields were normal. The left pupil was larger than the right; the corneal and gag reflexes were diminished. The tongue showed fibrillations, with slight deviation to the right. The cranial nerves were otherwise normal. The patient's mood tended to fluctuate between optimism and severe depression, with occasional episodes of increased irritability.

She was admitted to Montefiore Hospital on November 16. Neurologic examination then disclosed practically the same picture as that just described except that there was slight diminution of tactile sensation in both feet as compared with the rest of the body; pain and temperature sensations were diminished in both lower extremities below the knees and to a less extent in both hands. This diminution was somewhat patchy in its distribution, the patient occasionally calling "pinprick" dull in one area and sharp in an adjacent one. Vibratory sense was impaired, being absent in both feet, greatly diminished in both legs and slightly diminished as high up as the eighth thoracic dermatome. There was evidence of severe vasomotor disturbance in the hands and in the feet, which were cold, clammy and distinctly pale. There was profuse and continuous sweating on the palms and soles. There seemed to have been some astereognosis in both hands, but it was difficult to evaluate this because of the complete paralysis of the hands and fingers.

Sensory examination on November 27 disclosed vague sensory disturbances—hypalgesia and thermhypesthesia up to the tenth thoracic dermatome and loss in vibratory sensation in the lower extremities to about the knees.

In December 1936 the patient showed a tendency to gag on swallowing and difficulty in coughing. Atrophy of the muscles of the extremities became extreme, especially in the lower third of the thighs and in the hypothenar and thenar eminences. There were bilateral hand and foot drop and almost total areflexia. There were weakness of both trapezius and supraspinatus muscles and slight weakness of the sternocleidomastoid muscles. The abdominal reflexes were absent.

During her stay in the hospital the temperature, pulse and respiration were normal except terminally. Her blood pressure varied from 126 systolic and 80 diastolic to 140 systolic and 100 diastolic.

On November 21 reaction of degeneration was noted in most of the neuromuscular units. On December 7 the red glass test revealed weakness of the left internal rectus, the left superior and inferior rectus and the right superior and inferior rectus muscles. On Feb. 2, 1937 the patient began to complain of difficulty

*Data on the Spinal Fluid (1936) **

Date	Cells	Globulin	Protein, Mg./ 100 Cc.	Sugar, Mg./ 100 Cc.	Chlorides	Colloidal Gold Curve	Wassermann Reaction, 0.2 to 2 Cc.
5/27.....	3	+++	243	56	680	Negative
6/ 5.....	3	+	200	111122211
6/ 9.....	5	+++	94
6/30.....	2	++	125
7/14.....	3	+++	125	111122111	Negative
7/18.....	3	+++	250	75	765
7/22.....	3	+++	250	62	710
8/ 4.....	3	+++	200
9/12.....	5	++	113
10/17.....	9	++	112	222233311
11/16.....	4	+++	146	75	750	Negative

* There was no evidence of manometric block. The spinal fluid pressure measured from 90 to 200 mm.

in swallowing solid food; she salivated profusely and was cyanotic. Bronchopneumonia developed, and she died on February 7.

Laboratory Data.—The spinal fluid showed pronounced cytoalbuminous dissociation (table).

Repeated blood counts, chemical studies of the blood, serologic tests and urinalyses revealed nothing significant. The sedimentation rate was 18 mm. in one hour (September 1936). Special analyses for lead and arsenic gave results as follows:

Lead			
Blood, Mg./100 Gm. Solids	Urine, Mg./1,000 Cc.	Feces, Mg./100 Gm.	Spinal Fluid
May 29.....1.2	September 5....0.026	September 5....0.0	June 9.....0.0
September 5.....1.1	September 8....0.0	September 25....0.58	
September 9.....0.0	September 25....0.0	October 7.....2.5	
September 25.....0.85	October 7.....0.033	October 30.....1.05	
October 7.....2.4	October 30.....0.018	November 13....2.6	
October 30.....1.2			
November 13.....1.54			
Arsenic			
Blood, Mg./100 Gm.	Urine, Mg./100 Gm.	Feces, Mg./100 Gm.	
May 29.....0.037	June 6.....0.425	September 9.....0.0	
October 7.....0.0	September 8.....Trace	October 7.....0.022	
	October 7.....0.0		

No lead was found in the rouge or lipstick used by the patient. Her face powder contained 4.1 mg. of lead per 1.1 Gm. of powder. Specimens of the cold and hot water taken from her home contained no lead.

Although the quantity of lead in the blood was high, the amount of urinary lead was not. Analyses for arsenic did not reveal an abnormal amount except in the urine on June 6. These heavy metals were not believed responsible for the clinical picture presented by the patient.

Roentgenograms of the spine and skull revealed nothing abnormal.

The blood serum contained 1.81 Gm. of albumin and 2.15 Gm. of globulin. The basal metabolic rate was +3 per cent. Sweating tests showed no sweating below the umbilicus after one hour.

Treatment.—A variety of therapeutic measures were tried, to no avail. These included tonsillectomy (October 1936), intravenous injections of hypertonic solutions of dextrose and calcium carbonate, hyperthermia and a deleading regimen, i. e., institution of a low calcium, high phosphorus diet and administration of sodium thiosulfate by mouth. These measures accounted for the increase of lead in the excreta noted in the tabulation.

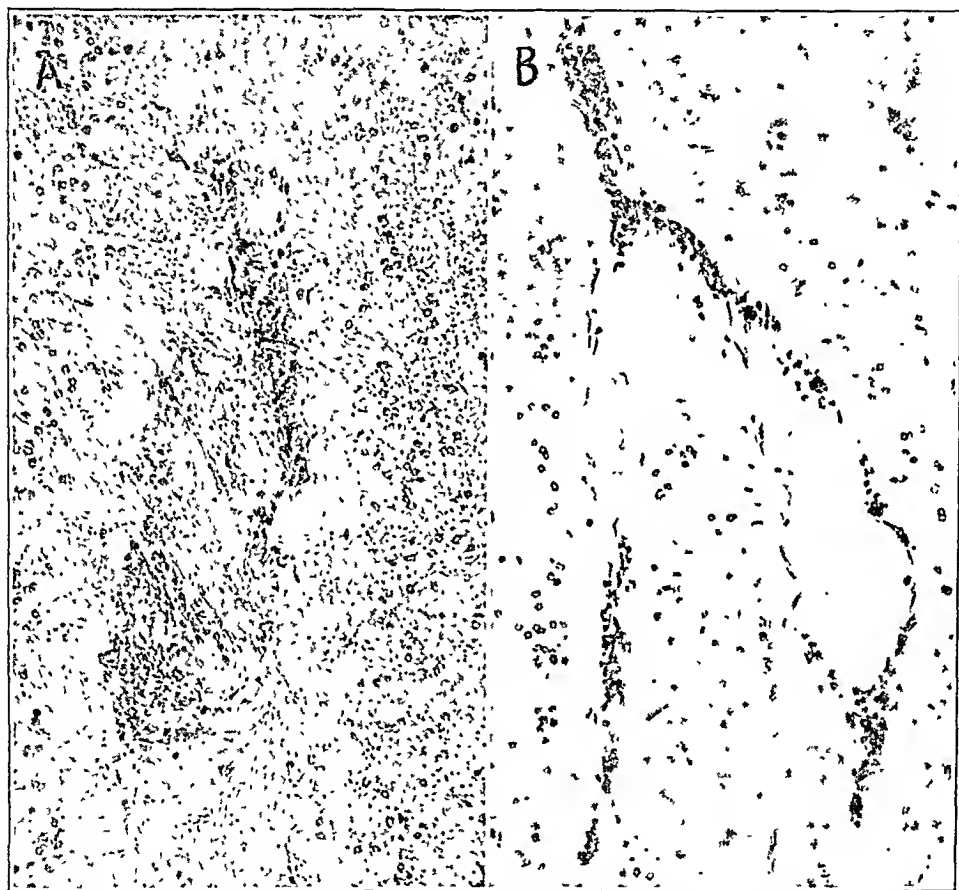


Fig. 1 (case 1).—*A*, iron deposits, few lymphocytes and area of destruction around the perivascular spaces in the cortex. *B*, inflammatory reaction in the hippocampus. Cresyl violet; $\times 100$.

Autopsy.—Gross Examination: The pia-arachnoid of the brain, especially over the frontal convolutions, had a dull, opaque appearance. The pia stripped readily. The cranial nerves appeared normal. The vessels of the white matter were slightly prominent.

The spinal cord showed no gross abnormalities. Various regions of the cord, including the conus medullaris and the cauda equina, and sections from the brachial plexuses, the right lumbar plexus and the left sciatic nerve were embedded for further study.

Microscopic Examination: Sections from various cortical regions; the optic nerves, chiasm and tracts, and the diencephalon, pons, medulla oblongata, cerebellum and dentate nuclei were stained by the myelin sheath and cresyl violet methods. Frozen sections of the spinal cord were also stained with the Spielmeyer and sudan III methods. The peripheral nerves were stained for myelin sheaths and by the Marchi, sudan III and Bielschowsky methods.

Cortex: The cortical sections, especially from the frontal and hippocampal regions, disclosed edema of the pia-arachnoid, with slight proliferation of the

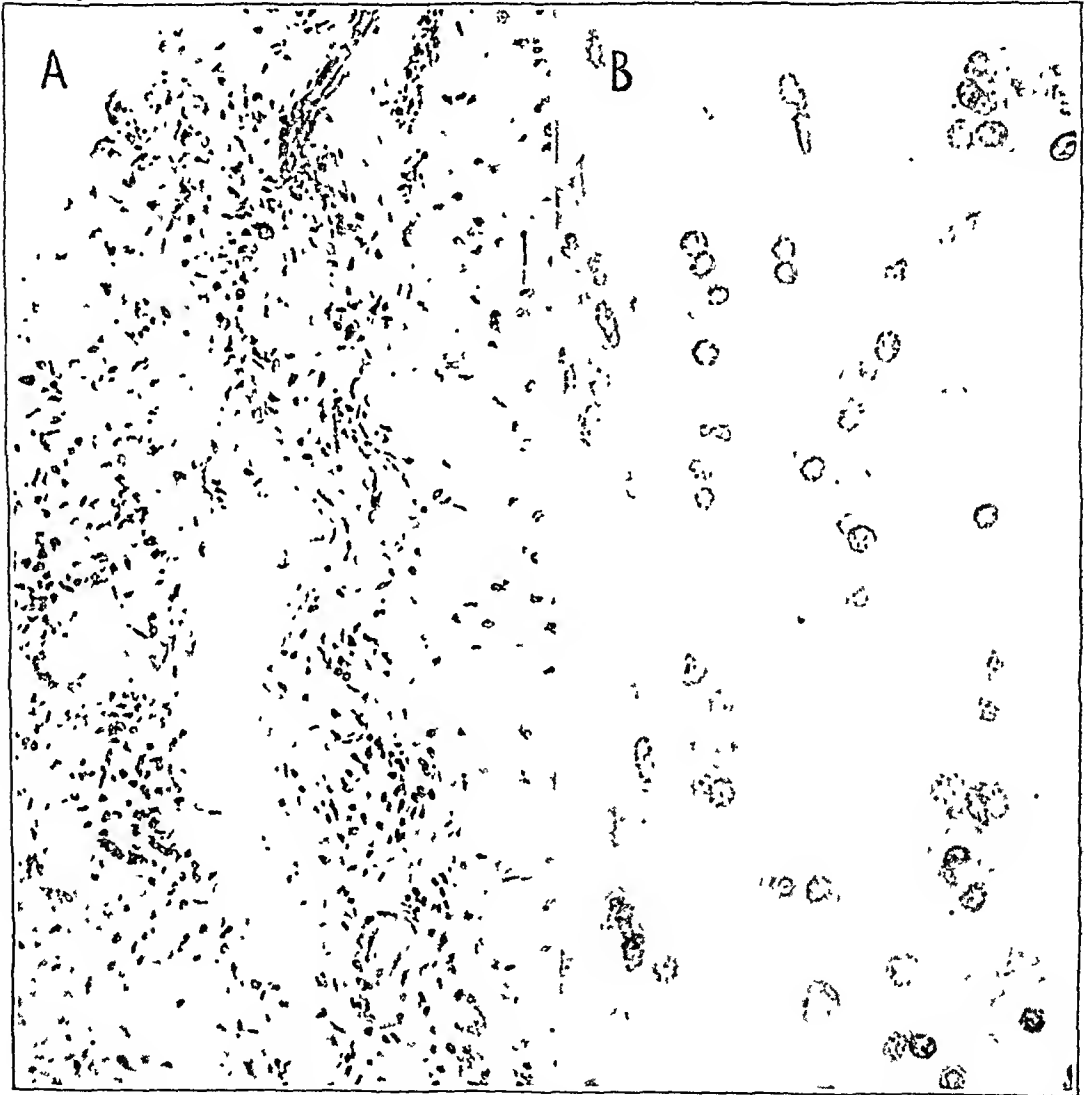


Fig. 2 (case 1).—*A*, meningeal reaction and extravasation of blood from the hippocampal area. *B*, neuronophagia and satellitosis of nerve cells of the hippocampus. Cresyl violet; $\times 400$.

arachnoidal cells but no inflammatory reaction. There was no distortion in the arrangement of the cytoarchitectural layers of the cortex, but the perivascular spaces of the cortex and the white matter contained deposits of iron and a few lymphocytes (fig. 1*A*). There were also small areas of devastation surrounding the vessels (fig. 1*A*). A few hippocampal vessels contained occasional lymphocytes and plasma and endothelial cells (fig. 1*B*). In one area the meninges of the hippocampus showed a slight inflammatory reaction, consisting of a few

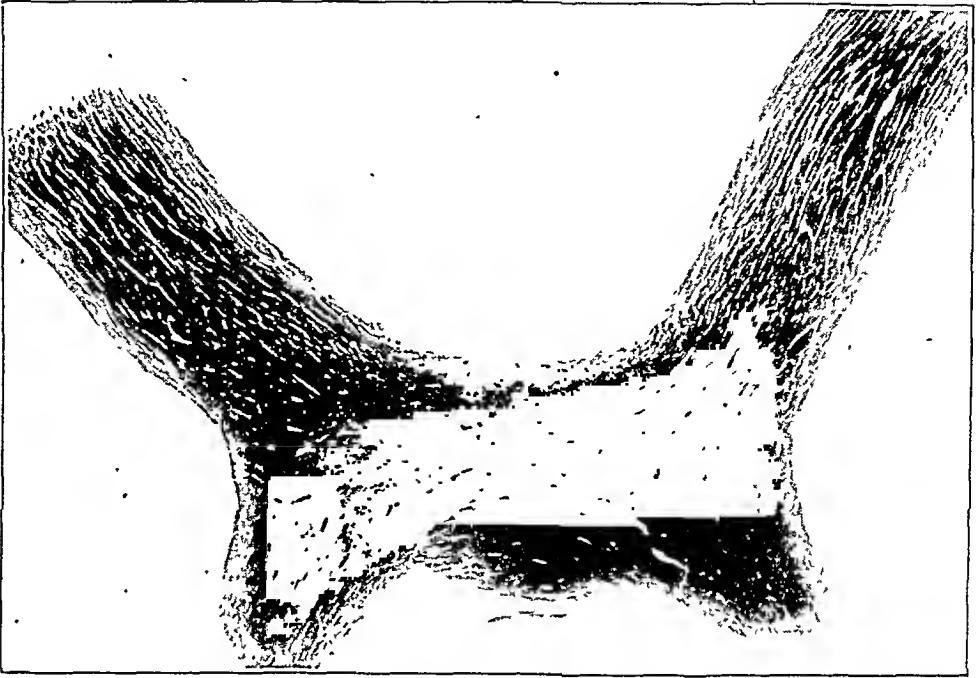


Fig. 3 (case 1).—Perivascular demyelination in the optic nerves.



Fig. 4.—Severe demyelination of practically all the roots in the sacral region.

lymphocytes, pigmentary deposits, reticuloendothelial cells and extravasation of red blood cells (fig. 2 *A*). Some of the nerve cells near the perivascular infiltrations showed beginning neuronophagia, satellitosis and other slight disintegrative changes (fig. 2 *B*).

Diencephalon and mesencephalon: There was nothing of note in the myelin sheath preparations. In the cresyl violet preparations a few vessels in the thalamus, hypothalamus, internal capsule, substantia nigra and mesencephalon showed the same perivascular reaction as was noted in the cortex. These infiltrations consisted of a mixture of inflammatory cells and compound granular corpuscles. The

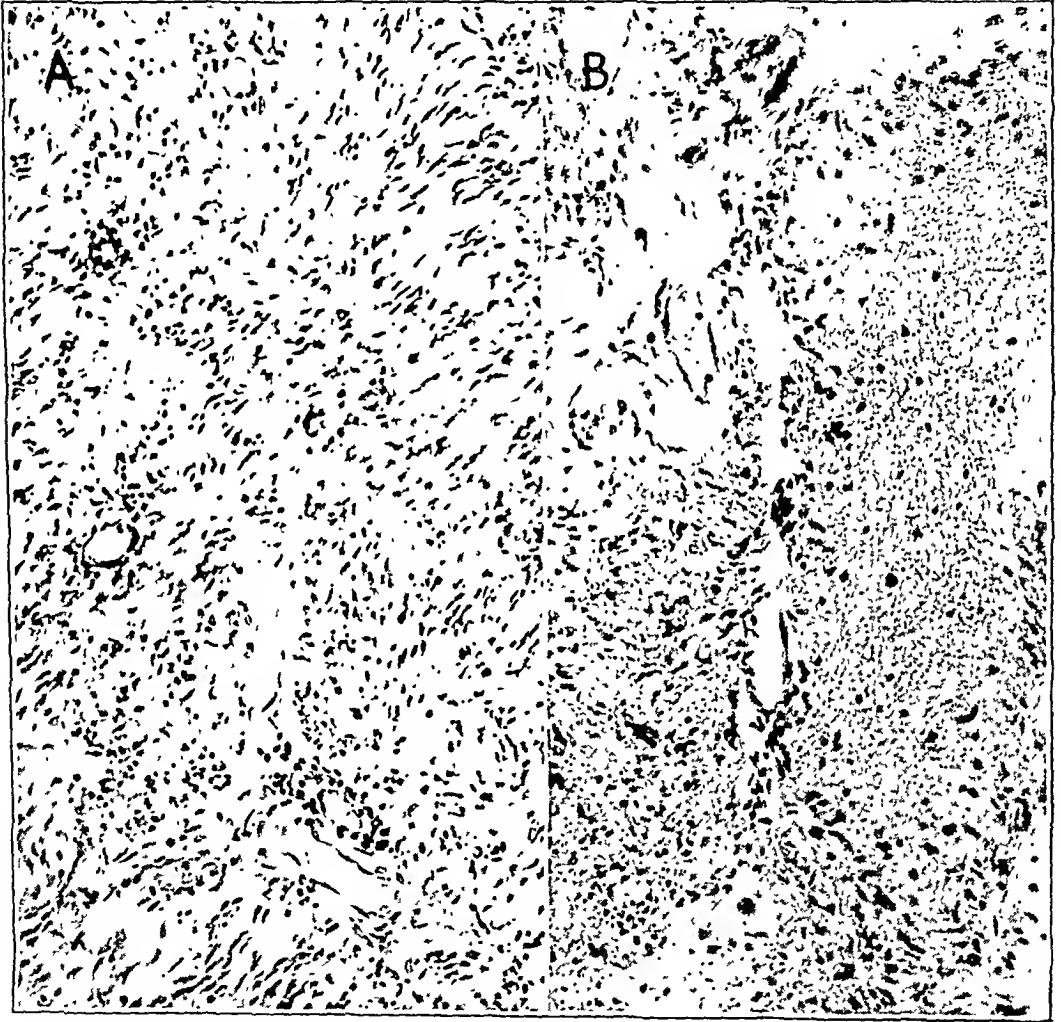


Fig. 5 (case 1).—*A*, perivascular infiltration and slight proliferation of vessels in the roots. *B*, necrosis of roots. Cresyl violet; $\times 100$.

perivascular infiltrations were more numerous in the cerebral peduncles. There was also an increase in microglia cells. Areas of demyelination, however, were not present.

Optic nerves and tracts: These structures, especially the tracts, disclosed perivascular demyelination with slight swelling of the myelin sheaths (fig. 3). Occasional perivascular infiltrations with lymphocytes and compound granular cells were observed in these regions. Holzer preparations revealed slight perivascular gliosis and astrocytic proliferation.

Pons: Sections of the pons through the nuclei of the third and fourth nerves disclosed the same slight perivascular infiltration as that seen in other regions. The ganglion cells near these areas disclosed neuronophagia and chromatolysis; this was best observed in nerve cells of the nuclei of the third and fourth nerves.

Medulla oblongata: The vessels of the pyramids and a few vessels on the upper pole of the olives showed a perivascular reaction similar to that seen in other parts of the central nervous system. Some of the nerve cells of the nuclei of the ninth and tenth nerves stained poorly and showed neuronophagia. There

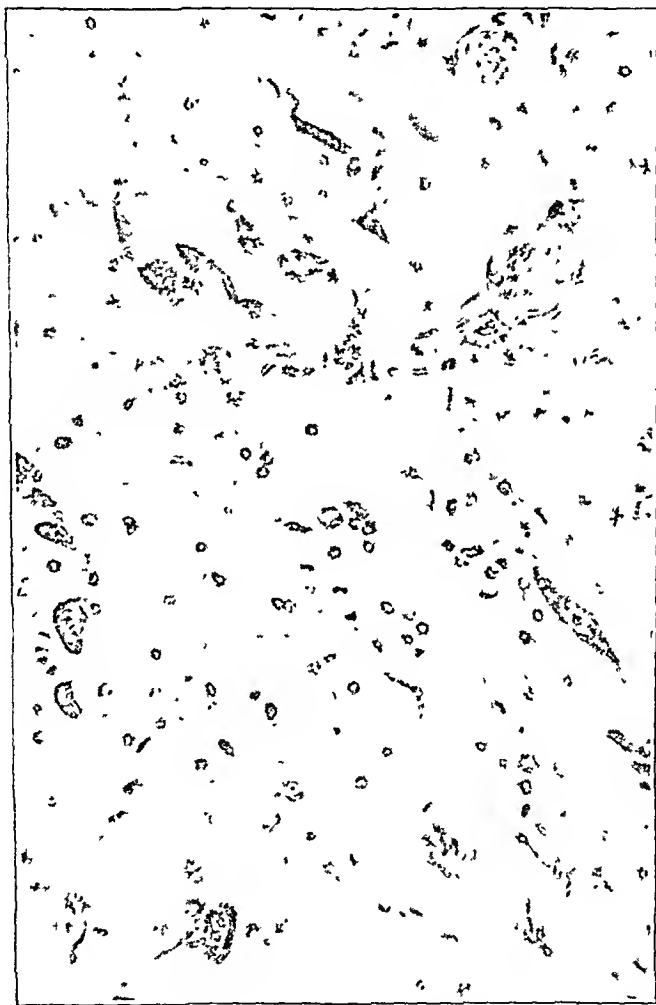


Fig. 6 (case 1).—Diminution in number and shrinkage of anterior horn cells. Cresyl violet; $\times 200$.

was a slight increase in the microglia cells in the region of the dorsal nucleus of the tenth nerve.

Cerebellum and dentate nucleus: A few vessels showed perivascular infiltrations. The Purkinje cells and the nerve cells of the dentate nuclei were well preserved.

Spinal cord: In the myelin sheath preparations the ventrolateral tracts, especially in the lower thoracic region, stained poorly as compared with the posterior tracts, but no changes could be demonstrated with any of the delicate

stains, such as the Marchi stain and sudan III. The roots, including their zones of entrance, were severely demyelinated throughout all regions. This was most pronounced in the sacral area (fig. 4). With the high power lens, hardly any myelin could be seen in these roots. The vessels of the roots were congested. There was also occasional proliferation of vessels, with deposits of iron pigment and lymphocytes (fig. 5A). The architectural arrangement of some of the roots was completely distorted, and other roots showed actual necrosis (fig. 5B). In the cresyl violet preparations the cervical region showed nothing of note.

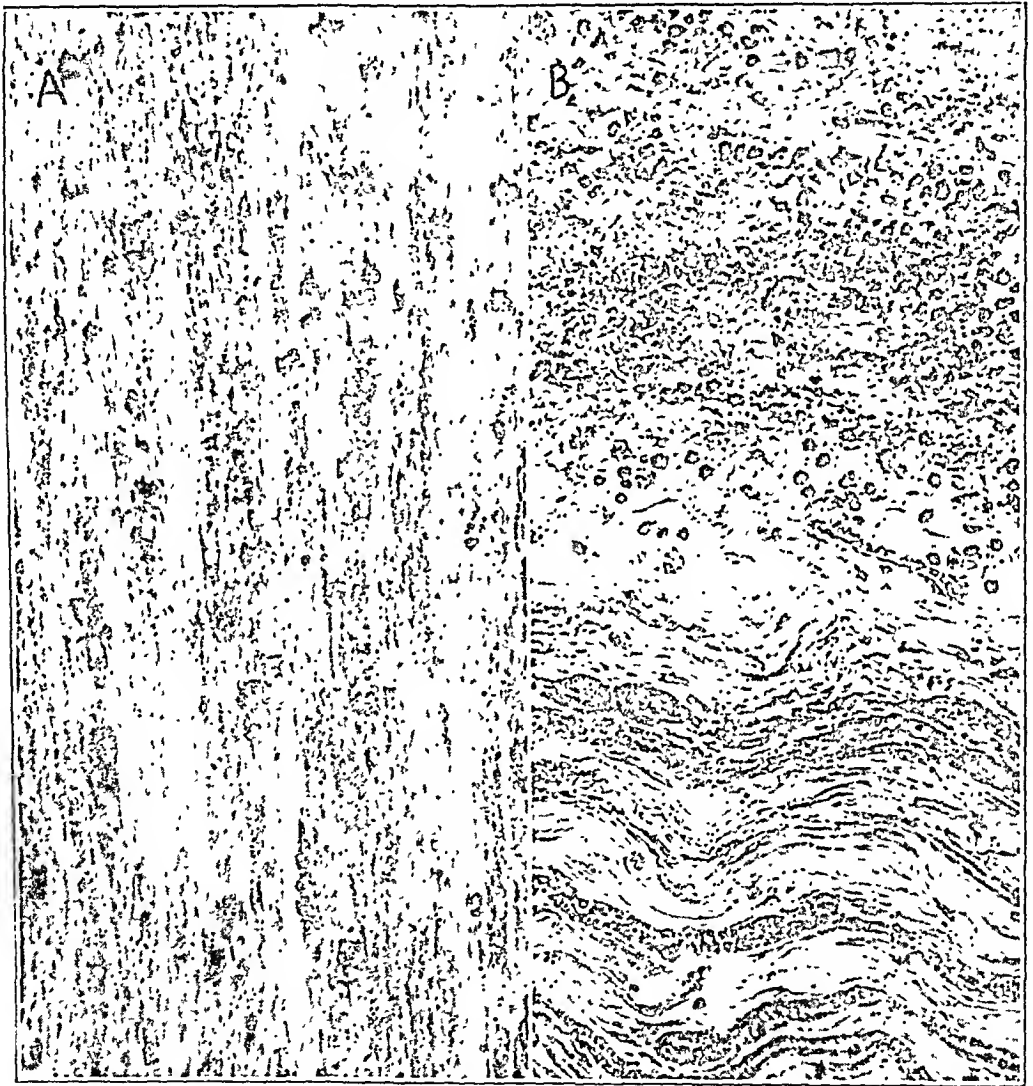


Fig. 7 (case 1).—A, breaking down of myelin, with deposition of fat; Marchi stain, $\times 70$. B, disintegration of myelin and inflammatory process within a peripheral nerve; sudan III, $\times 200$.

In the upper thoracic region there were edema of the pia-arachnoid and an inflammatory process of the meninges, consisting of lymphocytes, plasma and endothelial cells. An occasional nerve cell was shrunken. In the lower thoracic region there were notable diminution in number and shrinkage of nerve cells and increase in glia cells (fig. 6). The nerve cells of the sacral region also showed vacuolation.

Peripheral nerves: In the Marchi preparations there was disintegration of the myelin, with a few fatty globules, throughout all the nerves, most intense

in the brachial plexus and in the lumbosacral region (fig. 7 *A*). In the sudan III preparations, although there were no large deposits of fat in the conspicuously degenerated areas, the swollen nerve fibers and the fibers which were partly preserved disclosed fine lipid deposits, which stained paler than ordinary fat. Fat globules were also noted occasionally. The vessels of the nerves showed a collection of inflammatory cells, consisting of lymphocytes, plasma cells and endothelial cells (fig. 7 *B*). There were no iron deposits in these perivascular spaces. Some of the lymphocytes had actually penetrated the adventitia. The perineural

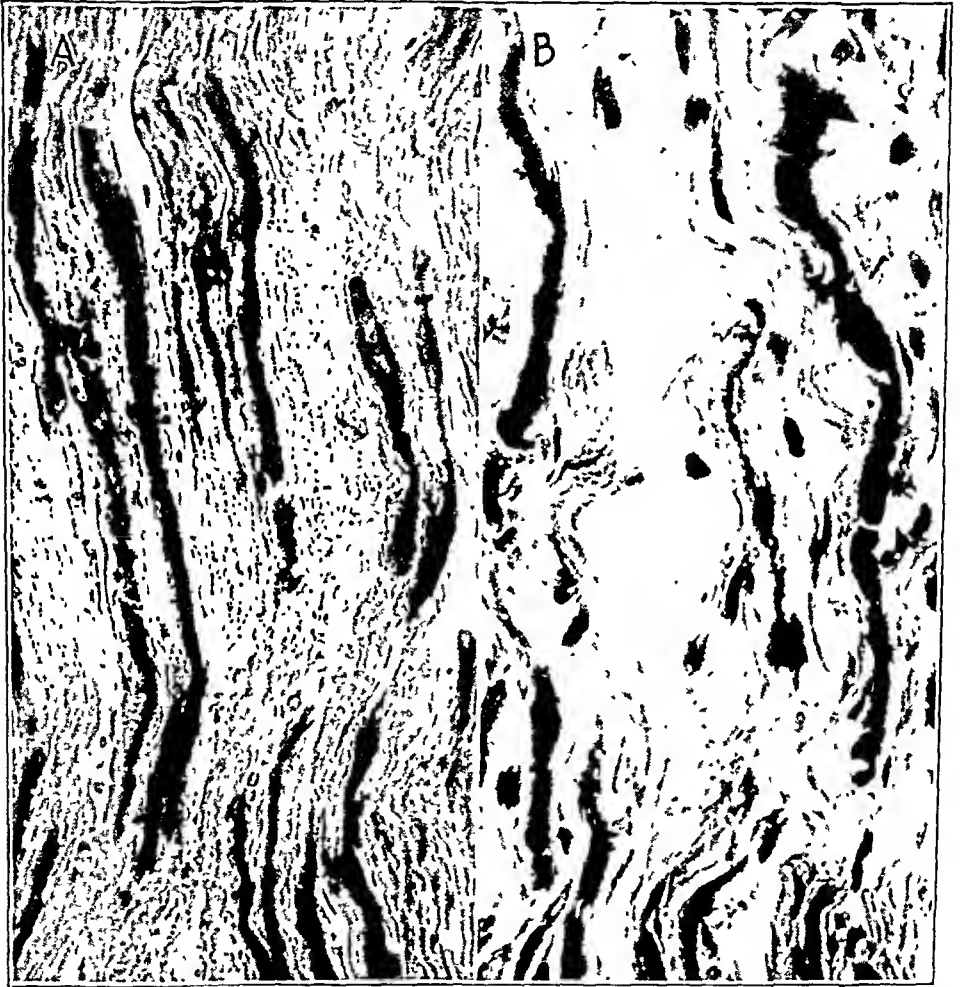


Fig. 8 (case 1).—*A*, destruction of myelin in peripheral nerves; Spielmeyer method, $\times 200$. *B*, extreme swelling and disintegration of the axis-cylinders, with bulbous process; Bielschowsky stain, $\times 400$.

spaces were loaded with lipid deposits. In myelin sheath preparations some of the myelin sheaths in various nerves, especially the sciatic, had completely disappeared; others were slightly swollen and fragmented (fig. 8 *A*). Still others were broken up and greatly swollen. There was hardly a normal fiber. In the Bielschowsky preparations the axis-cylinders disclosed disintegration, bulbous swellings and corkscrew processes (fig. 8 *B*). Swelling was the most prominent feature. In places inflammatory cells were seen.

Comment.—The lesions in this case were scattered throughout the entire nervous system, involving the cortex, mesencephalon, metencephalon, spinal cord, nerve roots and peripheral nerves. The pathologic process was severest in the roots and the peripheral nerves. The process was characterized by a mild inflammatory reaction throughout. The absence of early evidence of sensory disturbances may be due to the possibility that degeneration of the posterior roots took place late in the course of the illness.

The clinical picture in this case resembled that originally described by Guillain, Barré and Strohl except for the fatal termination. The laboratory findings were also similar.

CASE 2.⁶—J. K., a man aged 63, became ill about June 15, 1940. A dull pain appeared in the right shoulder; it soon spread and involved the right arm and then the left arm; within one week pain involved both lower limbs. The pain in the limbs was severe enough to awaken him at night. Numbness and weakness quickly beset the four limbs, especially the lower ones; the weakness forced him to take to bed. There was no paresthesia or muscular twitching and no defect in sphincter control. He was admitted to the Hospital for Joint Diseases on July 1, under the care of Dr. Martin Vorhaus. There was a past history of gonorrhea, syphilis, malaria and yellow fever in early adult life. At the age of 50 a cyst was removed from the thyroid.

On July 10 the patient was seen by one of us (S. B.). He presented the clinical picture of polyneuritis. The muscles of all the limbs were weak; all the deep reflexes were absent, as were the abdominal and cremasteric reflexes. Pressure on the calves elicited pain. All forms of sensation were diminished from the knees and elbows down. Facial weakness was present bilaterally, being more pronounced on the left side. There was hoarseness of recent onset, due presumably to weakness of the laryngeal muscles. (On July 2, indirect laryngoscopic examination did not reveal any visible lesion of the larynx or immobility of the vocal cords, but the examination was unsatisfactory because of gagging.) The cranial nerves were otherwise normal. Breathing was mainly abdominal. His blood pressure was 100 systolic and 60 diastolic.

During July 1940 some improvement appeared in the motor power of the upper limbs and weakness of the left side of the face decreased. About August 7 episodic mental confusion, with loss of memory, was noted. Orientation was retained. On August 18 the patient became irrational, agitated and disoriented. Mental confusion continued, being less at times. On August 30 he was disoriented and confused and kept repeating senseless phrases. Speech was unclear, hoarse and nasal, but the palate arched well. Facial paralysis was still evident, especially on the left. There was considerable wasting of all muscles of the limbs, and all the deep reflexes were absent. Breathing was mainly abdominal. Within the next few days, dyspnea, cyanosis and increased perspiration of the face and neck appeared. The patient became drowsy and finally comatose. On September 3 there was pitting edema of the left leg and a maculopapular rash appeared on the thigh. Bronchopneumonia and phlebitis of the left leg set in, associated with elevation of temperature to 103 F. A restless thrashing about, irrational behavior and screaming were clinical features. The temperature, pulse and respirations had been normal until August 29, when the temperature rose, ranging from 100.2 to 104 F. until

6. Dr. Martin Vorhaus gave us permission to report this case.

death; there was a preterminal rise to 106 F.; the Cheyne-Stokes type of breathing also preceded death.

Laboratory Data.—Several urinalyses revealed nothing significant. Three blood counts were reported as follows:

July 2: Hemoglobin, 13.5 Gm. per hundred cubic centimeters; red cells, 4,480,000, and white cells, 8,400, with 65 per cent segmented neutrophils, 4 per cent nonsegmented neutrophils, 3 per cent eosinophils, 1 per cent basophils, 26 per cent lymphocytes and 1 per cent monocytes.

August 28: Hemoglobin, 12 Gm. per hundred cubic centimeters; red cells, 4,000,000, and white cells, 7,800, with 70 per cent segmented neutrophils, 2 per cent eosinophils and 28 per cent lymphocytes.

September 11: Hemoglobin, 10.5 Gm. per hundred cubic centimeters; red cells, 3,680,000, and white cells, 11,700, with 78 per cent segmented neutrophils, 2 per cent nonsegmented neutrophils, 2 per cent eosinophils, 12 per cent lymphocytes and 3 per cent monocytes.

The sedimentation rate (July 11) was 12 mm. in one hour. On July 2 the Kahn and Kline reactions of the blood were negative.

Examination of the spinal fluid (July 2) revealed a clear fluid, under a pressure of 140 mm. of water. There was no evidence of block. The fluid showed a trace of globulin, 77 mg. of sugar per hundred cubic centimeters, negative reactions to the Kahn and Kline tests and a colloidal gold curve of 111100000. Unfortunately, no estimation of the protein content was made. Specimens of urine were sent to Dr. A. Gettler's laboratory for examination for the presence of heavy metals (lead and arsenic); none was found.

Autopsy.—General Observations: The diagnosis was bronchopneumonia, lower lobe of the right lung; organizing embolus in the right pulmonary artery; pulmonary congestion and edema; chronic pulmonary emphysema; coronary sclerosis; diverticulosis of the colon, and adenomatous polyps of the sigmoid.

Gross examination of Brain and Spinal Cord: No gross abnormalities were noted.

Microscopic Examination: Blocks from various cortical regions, the basal ganglia, the pons, the medulla oblongata and the spinal cord were embedded. Sections were cut and stained by the myelin sheath and cresyl violet methods. The peripheral nerves were stained by the Marchi, Weigert, Bodian and hematoxylin-eosin methods.

Cortex: No abnormalities were noted in the myelin sheath preparations. In the cresyl violet preparations the meninges showed slight thickening due chiefly to the presence of proliferating arachnoidal cells. The meningeal vessels showed moderate atherosclerotic changes. The cytoarchitectural layers of the cortex had a normal arrangement. An occasional engorged vessel was noted.

Diencephalon and basal ganglia: A few distended vessels were noted in the thalamic nuclei and in the putamen. No areas of demyelination were noted. In cresyl violet preparations the nerve cells of the putamen and the pallidum were normal. The perivascular spaces were somewhat distended. The nerve cells of the thalamus and hypothalamus were normal. There was pigment atrophy of some of the nerve cells of the hypothalamus. In sections through the pulvinar a few lacunas were noted. In the cresyl violet preparations numerous colon bacilli were noted in some of the vessels. A few vessels in this region were filled with lymphocytes.

Pons: Sections through the aqueduct of Sylvius showed no abnormalities in the myelin sheath preparations. In the cresyl violet preparations, there was some

pigment atrophy of the nerve cells of the nuclei of the ocular nerves and in some of the pontile nerve cells.

Medulla oblongata: No abnormalities were noted in the myelin sheath preparations. The cresyl violet preparations revealed a few amyloid bodies in the pyramids.

Cerebellum: Sections of this region disclosed slight swelling of the Purkinje cells.

Spinal cord: The myelin sheath preparations showed a slight pallor of the anterior roots at practically all levels. In the thoracic region there was also pallor

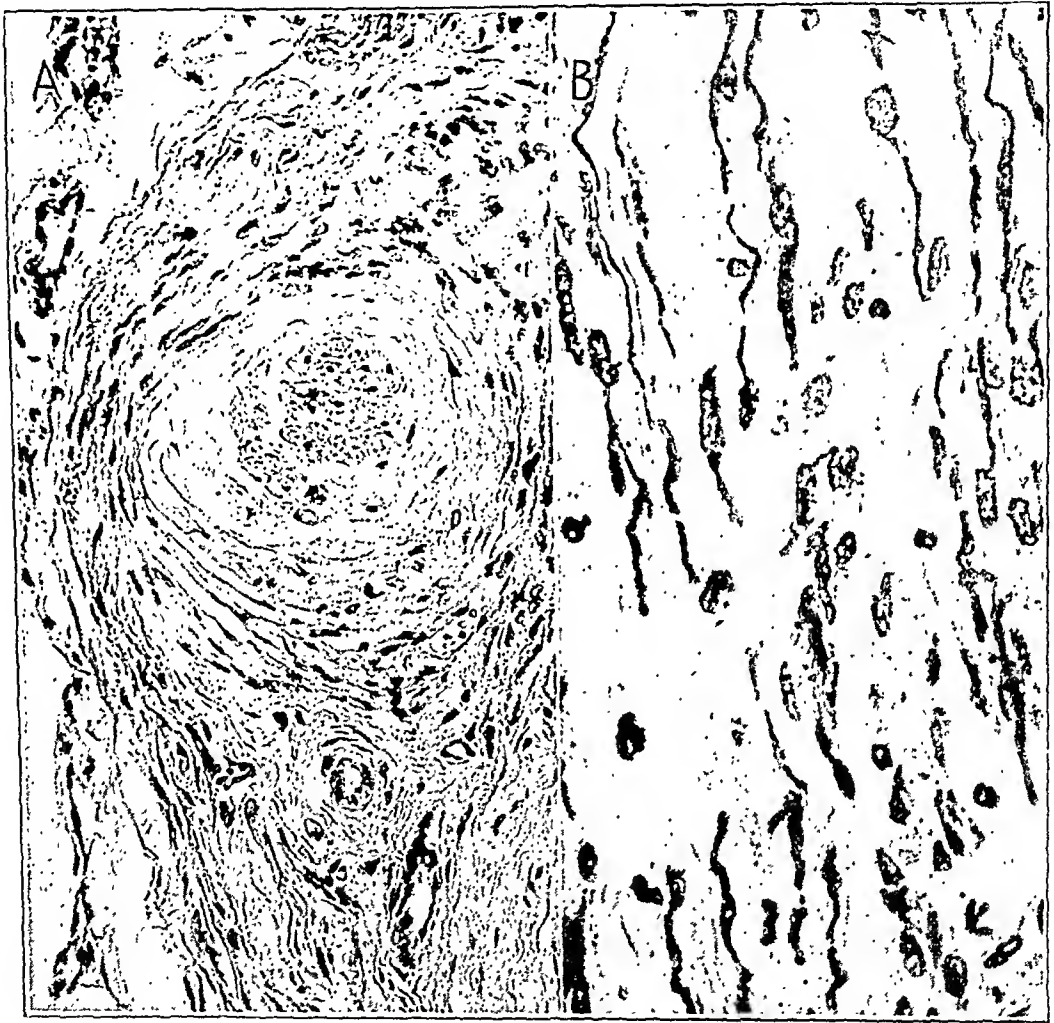


Fig. 9 (case 2).—*A*, onion-peel arrangement in a peripheral nerve; hematoxylin-eosin stain, $\times 150$. *B*, swelling and slight disintegration of axis-cylinders; Bodian method, $\times 400$.

of some of the posterior roots. Actual destruction of myelin sheaths could not be seen. In the gray matter of the midthoracic region there was dilatation of the perivascular spaces. Creyl violet preparations showed distention of the meninges without inflammatory reaction. The anterior horn cells were normal except for a few, which showed pigment atrophy. Some of the vessels of the gray matter were engorged. In some regions of the cord there were numerous amyloid bodies. In the lower thoracic region, one of the roots contained numerous psammoma bodies and two of the vessels in the posterior part of the cord showed atherosclerotic

changes, while two others showed hyaline degeneration. No actual pathologic change was noted in the cord at this level. In the lumbosacral region no abnormalities were noted except for pigment atrophy in the anterior horn cells. An occasional chromatolytic nerve cell was observed.

Peripheral nerves: The left brachial plexus showed destruction of the myelin sheaths. With the hematoxylin-eosin method, some of the nerve fibers in the right brachial plexus had an onion-peel arrangement (fig. 9 A), suggestive of that seen in progressive hypertrophic interstitial neuropathy (Dejerine-Sottas neuropathy). The demyelination was severe in the left posterior tibial nerves. With the Marchi stain, there was swelling of the Schwann nuclei. The blood vessels showed moderate atherosclerosis but no inflammatory changes. In places there was thickening of the perineural sheaths. The Bodian stain revealed breaking down, swelling and a corkscrew appearance of the axis-cylinders (fig. 9 B). The axis-cylinders were not so severely destroyed as the myelin sheaths. There was pronounced swelling of the Schwann nuclei at the periphery. Extensive changes were also observed in the right lumbosacral plexus. In the hematoxylin-eosin preparations there was swelling of the Schwann nuclei. The vessels showed moderate sclerotic changes. No inflammatory changes were noted. The perineural sheaths were thickened.

CASE 3.—D. G., a man aged 34, was admitted to the Montefiore Hospital on June 5, 1939, with a history of generalized weakness, inability to walk and loss of weight. His illness began in February 1938, though he had been easily fatigued for three years prior to this time. Weakness first appeared in the muscles of the calves; a month later his gait became awkward. In May 1938 he felt a burning pain in the soles, and in July of that year the skin of both legs below the knees became "purplish." The symptoms gradually grew worse. He was frequently awakened by severe pain. During this time he lost 25 pounds (11.3 Kg.) in weight, and a heavy pigmentation of the skin appeared "like a sunburn." In September 1938 he had an attack of angioneurotic edema, associated with a brief episode of bloody diarrhea, the cause of which could not be ascertained. There was no history of exposure to heavy metals or other injurious substances. The family history was not contributory.

He was admitted to the Neurological Institute of New York on Oct. 11, 1938 and discharged on Jan. 24, 1939. At that time examination disclosed weakness and atrophy of most of the muscles of the upper extremities, especially the pectoral, deltoid and triceps muscles; a mild defect in all types of sensation, with a fairly definite level at the junction of the thoracic and the lumbar dermatomes; loss of vibratory sensibility below the third lumbar vertebra, and hyperesthesia of the soles. When he was on his feet, there was cyanosis of the extremities. All the deep reflexes were absent except for a slight response of the biceps. Loss of muscular power was about 20 per cent in the lower extremities and 75 per cent in the upper extremities. His mental status was normal except for slight depression of mood.

Laboratory Data.—At the Neurological Institute of New York, the Wassermann reactions of the blood and the spinal fluid were negative. The spinal fluid was under normal pressure, with 110 mg. of total protein per hundred cubic centimeters; a reaction for globulin of 2 plus; 53 mg. of sugar and 670 mg. of chlorides, per hundred cubic centimeters, and a colloidal gold curve of 1111222321. Gastric analysis revealed a normal condition. Chemical analysis of the blood revealed 12.3 mg. of urea nitrogen, 84 mg. of sugar and 0.1 mg. of ascorbic acid, per hundred cubic centimeters. A five hour specimen of urine showed dextrose tolerance of 5 per

cent. The blood count was as follows: hemoglobin, 106 per cent; red cells, 5,660,000; color index, 0.9, and white cells, 10,650, with 67 per cent polymorphonuclear cells, 30 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. The sedimentation rate was 15 mm. in one hour. The serum chloride measured 570 mg. and the blood cholesterol 133 mg., per hundred cubic centimeters; the serum sodium, 138 mg. per liter; the blood calcium, 9.5 mg., and the blood phosphorus, 4.1 mg., per hundred cubic centimeters; the dextrose tolerance curve was normal. The fasting blood sugar was 78 mg. per hundred cubic centimeters. The serum protein was 6.9 Gm.; serum albumin, 4.3 Gm.; serum globulin, 2.6 Gm., and serum euglobulin, 0.4 Gm., per hundred cubic centimeters. The urine was normal except for 5 white cells per high power field. Analysis of the urine for lead gave negative results. On Oct. 10, 1938, the spinal fluid showed 7 cells per cubic millimeter, 168 mg. of total protein per hundred cubic centimeters, a 2 plus reaction for globulin and 64 mg. of sugar per hundred cubic centimeters. On November 3 the protein was 222 mg.; the reaction for globulin, 2 plus, and the sugar, 68 mg. per hundred cubic centimeters. Repeated examinations of the spinal fluid disclosed a similar picture. Examination of the stools showed nothing abnormal. Roentgenograms of the skull, vertebrae, chest and gastrointestinal tract showed a normal condition except that the shadow of the liver extended down somewhat farther than usual and the roentgenograms of the skull and the lumbar portion of the spine disclosed multiple areas of increased density, indicating the possibility of early Paget's disease (osteitis deformans). Peripheral vascular examination disclosed generalized dilatation of capillaries, due to disturbance in the vasoconstrictor mechanism, with resulting congestion of blood in venous capillaries and subcapillary plexuses.

At one time, a coarse nystagmus, more prominent on the right side, and a tendency to dorsiflexion of the left great toe were noted. Three times during the patient's stay at the hospital, angioneurotic edema of the face and tongue developed. This condition cleared up rapidly after epinephrine was administered. He was given high vitamin diet and large amounts of thiamine hydrochloride. He was transferred to Bellevue Hospital with the diagnosis of encephalomyeloradiculitis—Guillain-Barré type.

At Bellevue Hospital, examination disclosed the same clinical picture. Cutaneous temperatures indicated sympathetic paralysis of the lower extremities and partial dysfunction in the upper ones. The liver and spleen were palpable. The optic disks showed nasal blurring and congestion. Repeated examinations of the spinal fluid showed the protein-cellular dissociation, with total protein levels up to 200 mg. per hundred cubic centimeters. During the last two months of his stay at Bellevue Hospital, the patient showed considerable improvement in muscular power, so that he was able to take a few steps. Reactions to tests for allergy were negative for everything but ragweed. He was discharged to Montefiore Hospital on June 5, 1939.

At Montefiore Hospital, examination disclosed uniform gray-brown discoloration of the skin, with no pigmentation of the mucous membranes. The blood pressure was 126 systolic and 80 diastolic. The liver and spleen were palpable. Slight generalized lymphadenopathy was present. The extremities had a cyanotic hue, and the temperature was the same as that of the environment. There was moderate pitting edema of both lower extremities.

Neurologic examination disclosed generalized muscular atrophy, more advanced about the shoulder girdle and in the interosseous muscles of both hands; bilateral foot and hand drop, and contractures of the hands and feet. All the deep reflexes

and the abdominal and cremasteric reflexes were absent. The ulnar and common peroneal nerves were tender but not enlarged. There was pronounced diminution of all sensations in the upper and lower extremities, of the glove and stocking variety. Pseudoathetoid movements were present in the fingers, and a Chovstek sign was elicited. There were areas of "hyperpathia," especially about the right anterior cubital fossa and on both soles. Two point discrimination was slightly impaired in the hands.

The edema of the lower extremities was regarded as possibly due to renal disturbance or to changes in the lateral horn cells; pigmentary disturbances were attributed to endocrine imbalance, perhaps disease of the adrenal glands.

Laboratory Data.—Chemical analysis of the blood, including determinations of the calcium and phosphorus, gave normal values. Urinalysis, including tests for heavy metals and polyporphyrins, revealed nothing significant. Biopsy of the skin, like gastric analysis, revealed nothing unusual. A roentgenogram of the skull showed islands of increased density of bone. Repeated spinal punctures disclosed 6 to 8 cells per high power field, with protein as high as 222 mg. per hundred cubic centimeters.

Biopsy of the anterior tibial muscle showed mild atrophy.

Electroencephalographic tracings revealed no abnormal changes.

The patient was treated with various preparations of vitamins and hormones, to no avail. In January 1941 ascites appeared and abdominal punctures were done frequently. Examination of the ascitic fluid revealed nothing significant.

The liver and spleen continued to shrink, and just prior to death they were not palpable. The patient died on Feb. 12, 1942.

Autopsy.—General Observations: The diagnosis was hepatomegaly, splenomegaly, generalized lymphadenopathy, reticuloendotheliosis and generalized lymphocytic infiltration of various tissues.

The hyperplasia of the reticuloendothelial system in the absence of the universal round cell infiltration suggested to the pathologist a general low grade chronic infection, probably of virus origin. There seemed to be no relation between the hepatomegaly and splenomegaly and the peripheral neuropathy.

Gross Examination of the Nervous System: Brain: The pia-arachnoid had a glistening appearance. It was adherent to the convolutions but could be stripped readily. The pacchionian granulations were prominent. The vessels of the cerebral hemispheres were congested. The cranial nerves and the vessels at the base were normal. The white matter had an anemic appearance. No other gross abnormalities were noted.

Spinal cord: The spinal cord showed no gross abnormalities except for thinning. There was some translucency of the posterior columns.

Microscopic Examination of the Nervous System: Sections of the cortex, diencephalon, basal ganglia, mesencephalon, pons, cerebellum, medulla oblongata and spinal cord were stained by the myelin sheath and cresyl violet methods. Sections of the spinal cord and peripheral nerves were stained by the Marchi, Spielmeyer, sudan III and cresyl violet methods.

Cortex: In the myelin sheath preparations there was slight pallor of the white matter but no destruction of myelin sheaths. In the cresyl violet preparations the meninges were normal. The architectural arrangement of the cortex was normal. A few nerve cells showed water cell changes; no other abnormality was noted. In the white matter of the cortex there was occasional swelling of the oligodendroglia cells.

Diencephalon and basal ganglia: The myelin sheath preparations revealed slight pallor of the globus pallidus. With high power magnification, occasional

swollen myelin sheaths were noted in the pallidum. The striatum had a normal appearance. The large and small nerve cells stained normally. There were some calcified vessels and calcific deposits in the pallidum, surrounded by slight areas of devastation. There seemed to be disappearance of some nerve cells and a shadow-like appearance of others. The nerve cells of the hypothalamus were normal. The nerve cells of the substantia nigra did not contain the usual amount of pigment.

Midbrain and Medulla: Myelin sheath and cresyl violet preparations through the aqueduct of Sylvius showed no abnormality. Sections through the fourth ventricle

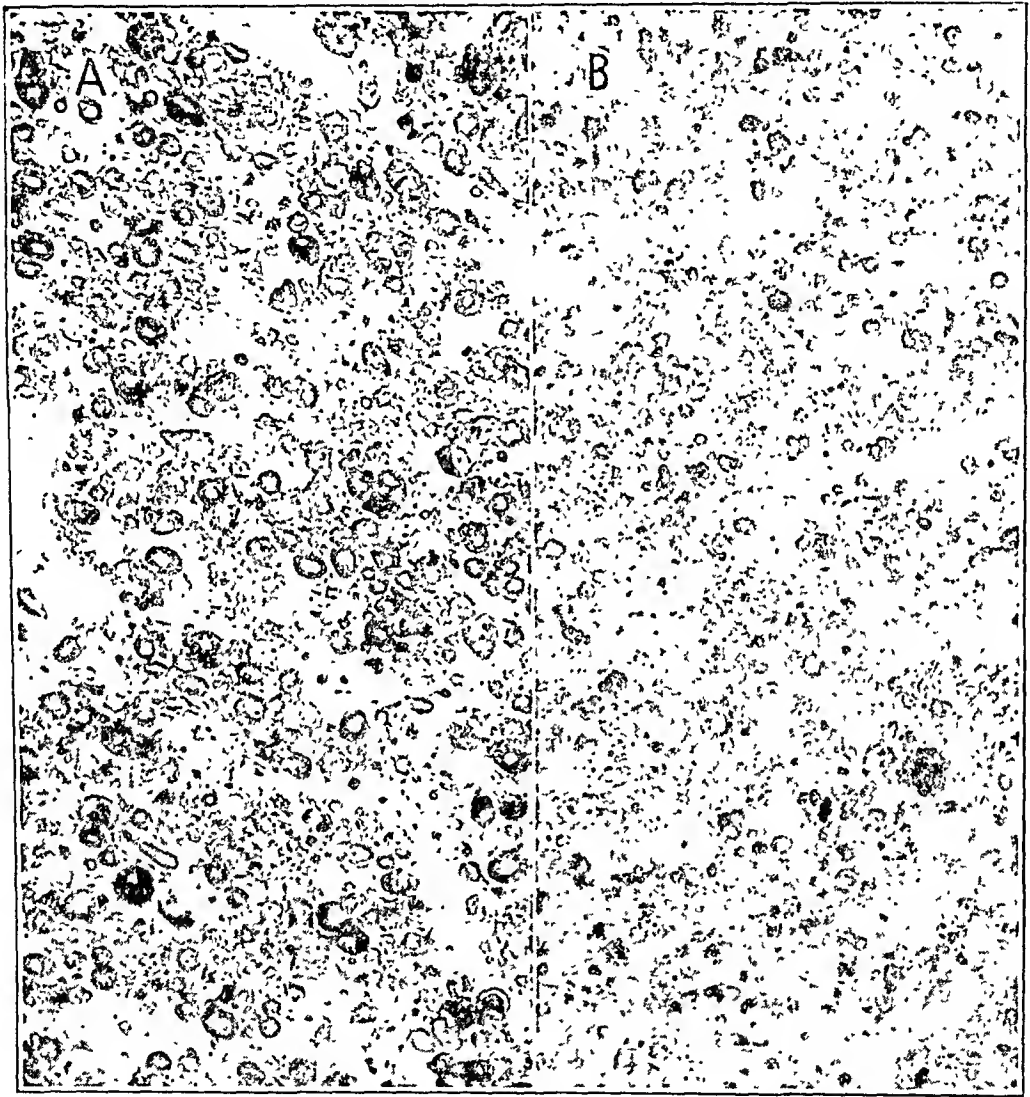


Fig. 10.—*A*, normal myelin sheaths in the posterior columns of the spinal cord. *B* (case 3), fatty globules in the posterior columns, to be compared with *A*; Marchi stain, $\times 200$.

revealed a normal condition. There was an occasional glial rosette in the region bordering the fourth ventricle. No other changes were observed in the medulla oblongata. In some sections of the cerebellum there was occasional perivascular infiltration, consisting of a few lymphocytes, plasma cells and endothelial cells. An occasional ischemic nerve cell was noted in the dentate nucleus. The Purkinje cells were within normal limits.

Spinal cord: No abnormalities were noted in the myelin sheath preparations except for an occasional swollen myelin sheath in the posterior columns of the lower thoracic region. In the sudan III preparations the same process was noted, but fat could not be demonstrated within the cord. The posterior roots showed occasional destruction and swelling of myelin. The anterior roots stained better than the posterior roots. In the Marchi preparations the dorsal columns of the lumbar portion of the cord showed breaking down of myelin and heavy black pigment granules (fig. 10 B). Some of the posterior and anterior roots also contained a few black granules. In the cresyl violet preparations there were amyloid bodies, especially in the posterior columns, and a slight increase in proliferating astrocytes. The meninges of the cord were distended but otherwise normal. In the gray matter there were numerous agonal hemorrhages, with slight breaking down of red blood cells in a few areas. The anterior horn cells amid these hemorrhages were well preserved. Here and there, an occasional chromatolytic nerve cell was noted.

Peripheral nerves: The Spielmeyer preparation showed severe destruction of some of the myelin sheaths and beading of others. The axis-cylinders showed swelling, disintegration and bulbous terminations. The architectural arrangement of almost every fiber was distorted. About half or more of the fibers had disappeared. In the Marchi preparations the same process was noted; with this stain numerous deposits of black granules could be demonstrated. The cresyl violet preparations showed elongation and proliferation of the nuclei of Schwann. There was also slight proliferation of the vessels.

COMMENT

Viets⁷ and Cobb and Coggeshall⁸ pointed out that cytoalbuminous dissociation may be found with other neuritides. In their analysis of the cerebrospinal fluid of 30 patients with infectious polyneuritis, Merritt and Fremont-Smith⁹ found a normal protein content in only 8 though the cell count was normal in 80 per cent. The presence of cytoalbuminous dissociation was definitely proved in 2 of our 3 cases. It varied from 94 to 240 mg. in case 1 and from 125 to 222 mg. per hundred cubic centimeters, in case 3. The protein content of the cerebrospinal fluid tends to increase in the acute phase of the disease, and this, according to our experience, may be observed not only with polyneuritis but also with many other diseases of the spinal cord. Indeed, the question may be raised whether the presence of cytoalbuminous dissociation has any particular etiologic importance.

Regarding the extent of the pathologic process beyond the peripheral nerves, Bradford, Bashford and Wilson demonstrated changes in the posterior roots, involvement of the nerve cells of the spinal cord with

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8. Cobb, S., and Coggeshall, H. S.: Neuritis, *J. A. M. A.* **103**:1608 (Nov. 24) 1934.

9. Merritt, H. H., and Fremont-Smith, F. F.: *The Cerebrospinal Fluid*, Philadelphia, W. B. Saunders Company, 1938.

perineural lymphocytic infiltration and a similar process about the nerve cells of the deeper layers of the cortex with very little neuronal change. Viets described changes in the nuclei of the seventh nerve and slight changes in the anterior horn cells of the spinal cord. Gilpin, Moersch and Kernohan¹⁰ mentioned changes in the posterior root ganglia and pontile nuclei in 1 of their cases. In their 3 fatal cases, Roseman and Aring¹¹ described the main pathologic process in the peripheral nerves. They also observed abnormalities in the spinal roots and ganglia, the cauda equina and the cells of the gray columns of the spinal cord (especially in the cervical and thoracic regions, with the greatest involvement of cells in the ventral gray columns) and some changes in the myelin sheaths and axis-cylinders in the pathways of the spinal cord. Involvement of the brain stem, especially the nerve cells of the olivary nuclei, the tractus solitarius, the nucleus ambiguus, the dorsal motor nucleus of the vagus nerve and the facial nuclei, and minor changes in the other cranial nerve nuclei were also described. Slight changes were also seen in various parts of the cortex and cerebellum. Roseman and Aring expressed the opinion that the changes in the central nervous system were of a readily reversible nature.

In our 3 cases widespread pathologic changes were observed, especially in case 1: The severest changes were seen in the peripheral nerves, those of next greatest intensity in the roots and spinal cord and those of least severity in the diencephalon and cortex. The optic nerves and tracts were involved in this case, accounting for the correlated clinical findings. In case 2, the spinal cord and higher neural structures were not involved. Interestingly, the changes in the peripheral nerves resembled slightly those seen in the Dejerine-Sottas type of hypertrophic neuropathy. The patient gave a history of early syphilis, but the serologic reactions were negative and clinical evidence of syphilitic involvement of the central nervous system was absent. In case 3, in addition to involvement of the peripheral nerves, there were changes in the spinal roots and posterior columns, slight perivascular infiltration in the cerebellum and glial rosette formation in the medulla oblongata.

115 East Sixty-First Street.

1155 Park Avenue.

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11. Roseman, E., and Aring, C. D.: Infectious Polyneuritis, *Medicine* **20**:463, 1941.

RELATION OF THE FRONTAL LOBE TO THE AUTONOMIC NERVOUS SYSTEM IN MAN

MAX RINKEL, M.D.

MILTON GREENBLATT, M.D.

GAYLORD P. COON, M.D.

AND

HARRY C. SOLOMON, M.D.
BOSTON

BILATERAL subcortical section of the frontal lobe of the brain was introduced to this country by Walter Freeman and James Watts¹ in 1936 for the treatment of serious mental conditions. In the course of the many hundreds of operations which have been performed, clinical observations have indicated a close relation of the frontal lobes to the autonomic nervous system. Sudden fall in blood pressure, relief from indigestion and palpitation, decrease in the blood sugar level, changes in gastrointestinal functions, sudden outbursts of rage, trembling, perspiration and occasional angioneurotic edema are some of the clinical observations after lobotomy which relate to the autonomic nervous system. Neurophysiologic investigations on animals in the past few years have uncovered fundamental facts with regard to cortical representations of the autonomic nervous system. Inhibition of respiration, rise of blood pressure and decrease in the tonus of the gastric musculature on electrical stimulation of the orbital surface of the frontal lobes in both cats and monkeys were reported by Bailey and Sweet.² Complex autonomic responses to excitation of the rostral part of the

This study was aided by a grant from the McCurdy Company, Rochester, N. Y.

Presented at the Seventy-Second Annual Meeting of the American Neurological Association, June 27, 1946, San Francisco.

From the Department of Psychiatry, Harvard Medical School, and the Boston Psychopathic Hospital, Dr. Harry C. Solomon, Director.

Able technical assistance was given by Miss Marie M. Healey and Mrs. Helen Mott, of the electroencephalographic laboratory, Boston Psychopathic Hospital.

1. Freeman, W., and Watts, J. W.: *Psychosurgery*, Springfield, Ill., Charles C Thomas, Publisher, 1942.

2. Bailey, P., and Sweet, W. H.: Effects on Respiration, Blood Pressure and Gastric Motility of Stimulation of Orbital Surface of Frontal Lobe, *J. Neurophysiol.* 3:276-281 (May) 1940.

cingulate gyrus, Brodman's area 24, were obtained by Smith³ in the monkey *Macaca mulatta*. Kennard,⁴ by means of the ablation technic, investigated corticoautonomic representations in cats and monkeys. In the cat, bilateral removal of the frontal lobe is followed by all the symptoms of sham rage. In the monkey, similar signs of release of autonomic function follow the same procedure, but no sham rage results. The subcortical bilateral prethalamic section of the frontal lobe for psychosurgical reasons presented an opportunity to investigate in man the relation of the frontal lobes to the autonomic nervous system.

METHOD OF INVESTIGATION

A total of 95 patients were examined, of whom 29 had undergone prefrontal lobotomy. The control group consisted of 14 volunteer medical students and nurses and 52 hospital patients. A number of the latter had received various forms of shock treatment.

The autonomic nervous system was tested (1) pharmacologically and (2) by stimulation of the carotid sinus. The pharmacologic test was restricted to the intravenous injection of 0.05 mg. of epinephrine hydrochloride (1:1,000), which ordinarily causes only a slight change in blood pressure and pulse rate, and little or no untoward reaction. The effects of cholinergic drugs are not reported because of the difficulty encountered in preliminary experiments in evaluating their comparative effects. Reitman⁵ evidently had the same difficulty, judging by the inconclusive results that he reported in a preliminary paper. We, therefore, have used the carotid sinus reflex as a method to test the functions of the parasympathetic system. The result of stimulation of the carotid sinus is unequivocal, and positive reflexes are rare among normal persons. Furthermore, since neither the immediate afferent or efferent pathway of the carotid sinus reflex arc is affected by lobotomy, it could be assumed that a pronounced increase in the incidence of the positive carotid sinus reflex in lobotomized patients would provide information concerning the functions of the frontal lobes. The effect of unilateral and of bilateral stimulation of the carotid sinus was observed clinically and by means of simultaneous electrocardiographic and electroencephalographic tracings.

RESULTS

The Sympathetic Nervous System.—This system responded to the intravenous injection of 0.05 mg. of epinephrine hydrochloride (1:1,000) differently in patients on whom lobotomy had been performed and in hospital patients who had not undergone this operation. Also, there was a striking difference in the reactions of the same patient when he was tested before and after the operation. Table 1 shows the effect of

3. Smith, W. K.: The Functional Significance of the Rostral Cingular Cortex as Revealed by Its Responses to Electrical Excitation, *J. Neurophysiol.* 8:241-255 (July) 1945.

4. Kennard, M. A.: Focal Autonomic Representation in the Cortex and Its Relation to Sham Rage, *J. Neuropath. & Exper. Neurol.* 4:295-304 (July) 1945.

5. Reitman, F.: Autonomic Responses in Prefrontal Leucotomy, *J. Ment. Sc.* 91:318-321 (July) 1945.

intravenous injection of 0.05 mg. of epinephrine hydrochloride on the systolic blood pressure, the height of which was reached within one minute. The average increase in the systolic blood pressure in patients with lobotomy was 85.1 mm. of mercury, as compared with 42.4 mm. in patients of the hospital who had not been operated on. Table 1 also shows that patients were tested from four to one hundred and twenty days after the operation but that the time interval had no effect on the response. There was a slight difference in the reactions of patients who had received electric or insulin shock treatment; however, the number

TABLE 1.—*Rise in Systolic Blood Pressure of Patients With and Without Lobotomy on Intravenous Injection of 0.05 mg. of Epinephrine Hydrochloride*

Hospital Patients							
Record No.	Mm. Hg	Time of Reaction, Min.	After EST : IST *				
			Record No.	Mm. Hg	Time of Reaction, Min.		
7	50	1	2	30	1		
	50	1	3	20	1		
	60	1	4	50	1		
	40	1	5	60	1		
	40	1	6	20	2		
	50	1	9	30	1		
	45	1	18	50	1		
17	40	1	19	30	1		
27	50	1	69	50	1		
Average: 47.2 mm.			Average: 37.7 mm.				
Total average: 42.0 mm. Hg							
Patients After Lobotomy							
Record No.	Mm. Hg	Time of Reaction, Min.	Days After Operation	Record No.	Mm. Hg	Time of Reaction, Min.	Days After Operation
1	60	1	13	20	120	1	26
	70	1	68	22	70	1	26
4	80	1	4	21	90	1	26
	110	1	8	26	100	1	27
	92	1	24	43	70	1	16
9	70	1	13	44	80	1	8
11	100	1	20	54	80	1	17
18	90	2	25	59	80	1	5
Total average: 85.1 mm. Hg							

* EST and IST indicate previous electric and insulin shock treatments.

of patients tested was too small to allow any conclusive deductions. Table 2 demonstrates the difference between the rise of the pulse pressure in the lobotomized patients, with an average of 60.8 mm. of mercury, and that in the control group, with an average of 26.3 mm. Pilomotor reactions and shivering were more frequently observed in patients on whom lobotomy had been performed.

The notable difference in the response to epinephrine hydrochloride (0.05 mg., given intravenously) is accentuated by a comparison of the effects in the same patient before and after lobotomy (fig. 1).

On the basis of these observations, the question arises whether the greater reaction of the sympathetic nervous system after lobotomy

is due to an elimination of vagal inhibition. In favor of this theory are the following facts: 1. Similarity in rise of the systolic blood pressure induced with epinephrine in patients after lobotomy and in normal persons after inhibition of the vagus nerve with atropine (fig. 2). 2. Relation of the orbital surface of the frontal pole to vagal function. Kennard⁶ reported that bilateral removal of this region in

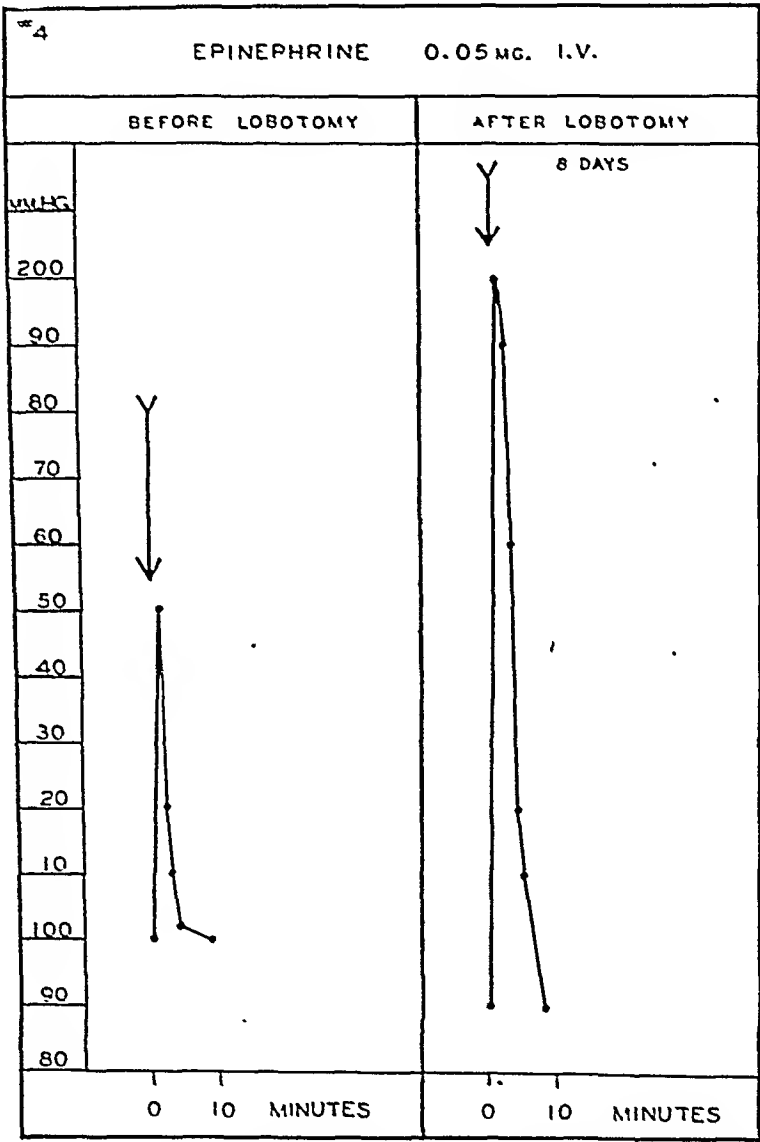


Fig. 1.—Responses to intravenous injection of 0.05 mg. of epinephrine hydrochloride before and after lobotomy. The arrow marks the point at which epinephrine was injected.

cats caused panting, increase in heart rate and increased production of epinephrine, as shown by the denervated iris and the nictitating membrane.

6. Kennard, M. A.: Autonomic Functions, in Bucy, P. C.: The Precentral Motor Cortex, Urbana, University of Illinois Press, 1944, p. 304.

In our patients, however, there was no blocking of the vagus nerve or elimination of vagal inhibition, as direct examination of the vagus system revealed.

Vagus or Parasympathetic Nervous System.—This system was tested by stimulation of the carotid sinus. Our experiments revealed a dramatic effect, consisting of three groups of reactions in sequence: (1) slowing of the heart to the point of cardiac arrest, (2) high voltage slow waves in the 2 to 5 per second range of frequency in the electroencephalogram

TABLE 2.—*Rise in Pulse Pressure of Patients With and Without Lobotomy on Intravenous Injection of 0.05 Mg. of Epinephrine Hydrochloride*

				After EST : IST *			
No.	Initial Pulse Pressure, Mm.	Height of Reaction, Mm.	D †	No.	Initial Pulse Pressure, Mm.	Height of Reaction, Mm.	D †
7	40	100	60	2	70	80	10
	50	80	30	3	60	60	0
	50	80	30	4	30	30	0
	70	100	30	5	30	70	40
	60	90	30	6	50	70	20
	50	80	30	9	40	60	20
	60	95	35	18	40	70	30
17	40	70	30	19	40	70	30
27	60	90	30				
Average: 33.9 mm.				Average: 18.7 mm.			
Total average: 26.3 mm. Hg ‡							
Patients After Lobotomy							
No.	Initial Pulse Pressure, Mm.	Height of Reaction, Mm.	D †	No.	Initial Pulse Pressure, Mm.	Height of Reaction, Mm.	D †
1	40	90	50	20	30	140	110
	30	90	60	21	30	90	60
4	30	100	70	22	40	70	30
	30	120	90	26	30	110	30
	40	80	40	43	40	100	60
9	40	110	70	44	30	90	60
11	70	120	50	54	30	90	60
18	30	90	60	59	30	100	70
Total average: 60.6 mm. Hg ‡							

* EST and IST indicate previous electric and insulin shock treatments.

† D is the difference between the basal and the highest pulse pressure.

‡ The total average refers to the difference between the basal and the highest pulse pressure.

and (3) loss of consciousness with tonic-clonic convulsions (figs. 3 and 4).

Patients Undergoing Lobotomy: Twenty-five such patients were compared with 40 control patients on whom no operation was performed. Table 3 shows that on stimulation of the carotid sinus the electrocardiogram recorded a positive effect in 84 per cent of the patients operated on, as compared with 63 per cent of the control group. Among those undergoing lobotomy, the incidences of a slight to moderate slowing of the heart (+ to ++) and very marked slowing or cardiac arrest (+++ to ++++) were about equal, i.e., 44 and 40 per cent, whereas for the control group the values were 40 and 22.5 per cent respectively.

From these figures, it can be seen that on stimulation of the carotid sinus in patients after lobotomy the incidence of a maximal cardiac reaction was about twice that for the control group. This observation permits the conclusion that in the patients operated on the vagus system responds readily to appropriate stimulation, in fact, more readily (84 as compared with 63 per cent) and with greater intensity (40, as compared with 22.5 per cent) than in the control group.

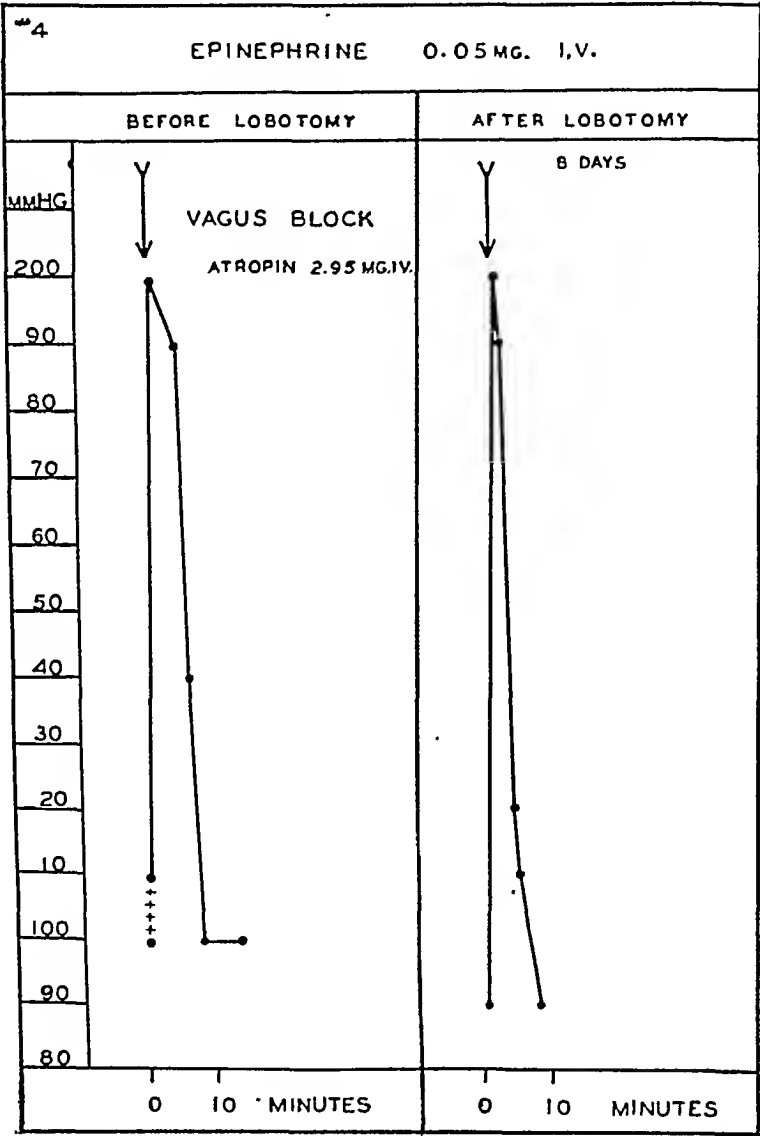


Fig. 2.—Rise in blood pressure on intravenous injection of 0.05 mg. of epinephrine hydrochloride after lobotomy, as compared with the effect on the blood pressure of a normal subject after block of the vagus nerve by intravenous injection of 2.95 mg. of atropine sulfate. The arrows mark the point at which the epinephrine was injected.

In 9 instances we were able to compare the effect of stimulation of the carotid sinus in the same patient before and after lobotomy. The results, as recorded in table 4, show that in all patients the carotid sinus

reflex became positive after lobotomy. Again, there was the intensified effect on the heart.

Observations, therefore, on the effect of stimulation of the carotid sinus in patients who have undergone lobotomy clearly reveal that in human subjects the severance of the frontal lobes neither eliminates nor blocks the vagus system.

Electroencephalographic recordings demonstrated that 92 per cent of the patients operated on had high voltage slow waves in the 2 to 5 per second range of frequency, as compared with 50 per cent for the control group. Also, the clinical signs, namely, loss of consciousness and

TABLE 3.—*Effect of Stimulation of the Carotid Sinus in Patients Who Have Undergone Lobotomy*

	Hospital Patients (No Operation)	Patients After Lobotomy
Number of patients.....	40	25
Electrocardiogram.....	25 (63%)	21 (84%)
Effect on heart rate *		
+ - ++.....	16 (40%)	11 (44%)
+++ - +++++.....	9 (22.5%)	10 (40%)
Electroencephalogram †.....	20 (50%)	23 (92%)
Clinical signs ‡.....	17 (42%)	22 (88%)

* + - ++ indicates slowing of the heart (increased QRS interval); +++ - +++++, heart arrest.

† Figures indicate the incidence of high voltage slow waves in the electroencephalogram.

‡ Clinical signs included unconsciousness and tonic-clonic convulsions.

TABLE 4.—*Effect of Stimulation of the Carotid Sinus on Nine Patients Before and After Lobotomy*

	Before Lobotomy	After Lobotomy
Electrocardiogram.....	5 (55.5%)	9 (100%)
Slowing of heart *		
+ - ++.....	5 (55.5%)	3 (33.3%)
+++ - +++++.....	0	6 (66.6%)
Electroencephalogram †.....	6 (66.6%)	9 (100%)
Clinical signs ‡.....	5 (55.5%)	9 (100%)

* + - ++ indicates slowing of the heart (increased QRS interval); +++ - +++++, heart arrest.

† Figures indicate the incidence of high voltage slow waves in the electroencephalogram.

‡ Clinical signs included unconsciousness and tonic-clonic convulsions.

short-lasting tonic-clonic convulsions, were more frequently observed in the patients undergoing lobotomy (88 per cent) than in the control group (42 per cent).

Control Group: To establish a control group, we examined 52 hospital patients who had not undergone lobotomy, but many of whom had received various forms of shock treatment. Since stimulation of the carotid sinus resulted in an unusually high percentage of positive reactions, we attempted to obtain normal controls by enlisting the cooperation of 14 medical students and nurses. Seven of these 14 subjects exhibited only slight electrocardiographic and electroencephalographic

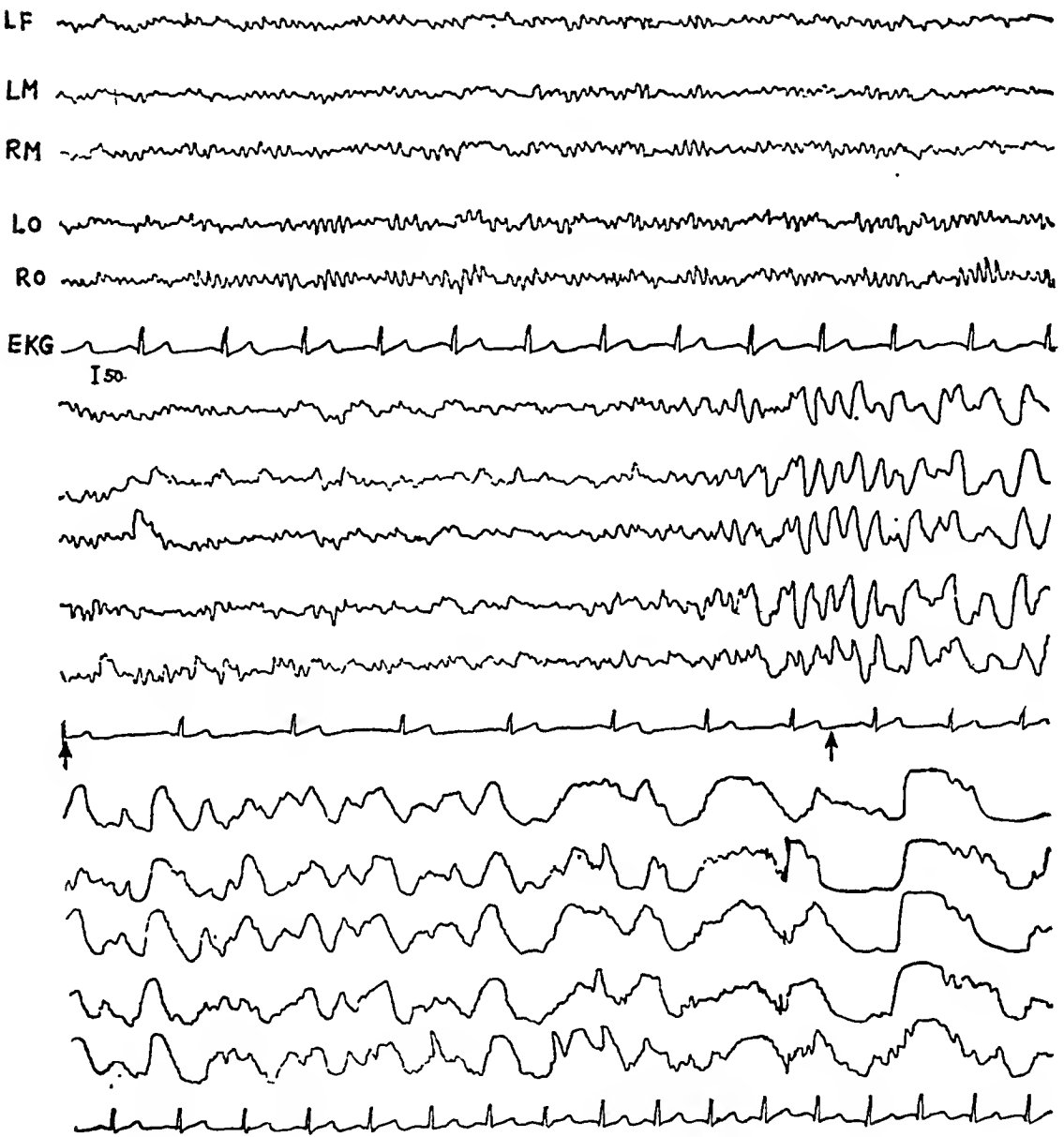


Fig. 3.—Continuous electroencephalographic and electrocardiographic recordings, with effects of bilateral stimulation of the carotid sinus.

The electroencephalographic leads are indicated as follows: *LF*, left frontal area; *LM*, left motor area; *RM*, right motor area; *LO*, left occipital area; *RO*, right occipital area.

EKG, indicates the electrocardiogram, with electrodes placed on the right and left sides of the upper part of the chest.

The upright marker indicates 50 microvolts. Each strip of record represents ten seconds.

The first arrow marks the beginning of stimulation of the carotid sinus; the second arrow, the end of stimulation and the beginning of convulsions, which lasted about twelve seconds. The electrocardiogram immediately after beginning of stimulation shows moderate slowing of the heart, which is followed by increased heart rate.

The electroencephalogram, about seven seconds after beginning of stimulation, shows high voltage slow waves, which appear from all cortical areas.

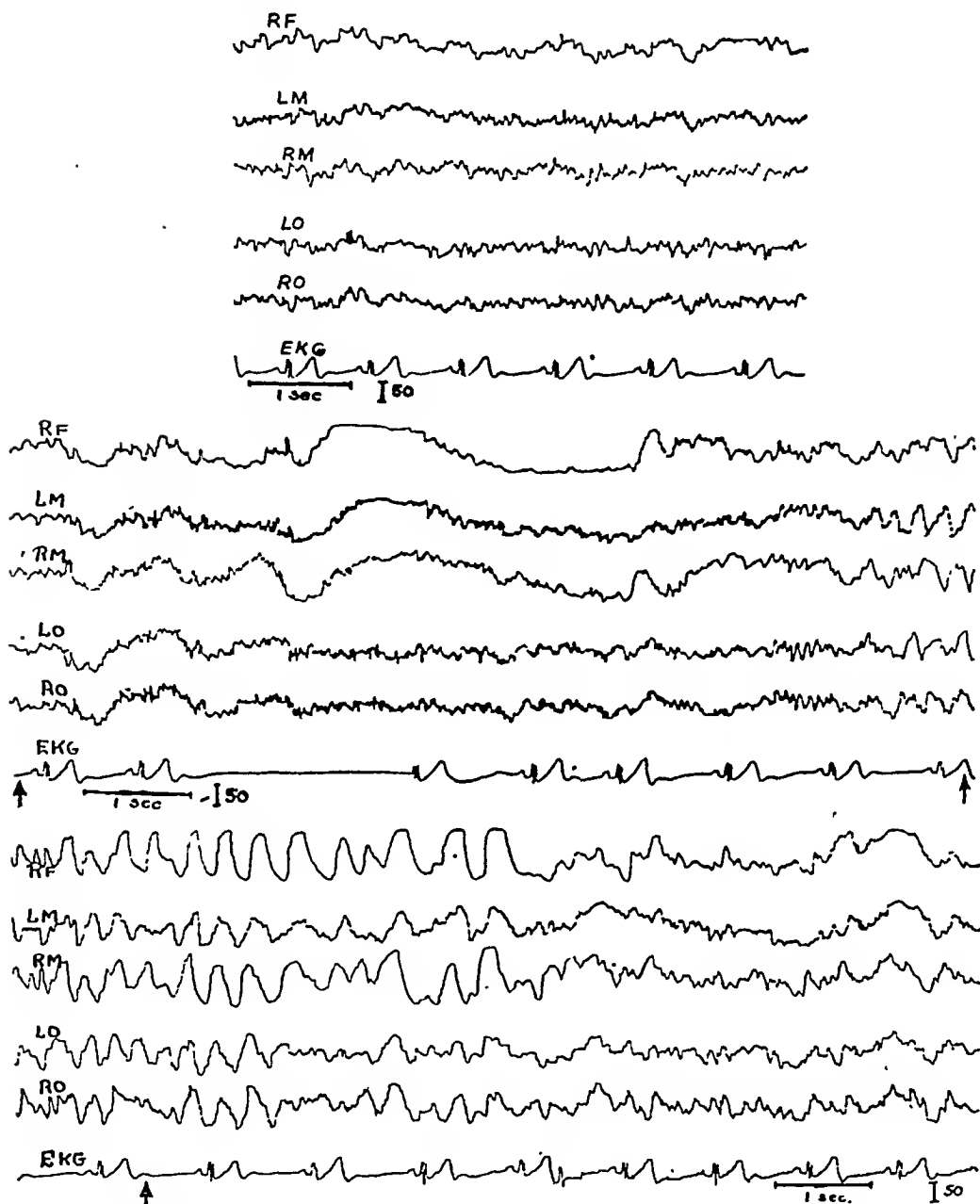


Fig. 4.—Continuous electroencephalographic and electrocardiographic recordings, showing effects of bilateral stimulation of the carotid sinus for ten seconds (interval between arrows).

The electroencephalographic leads are indicated as follows: *RF*, right frontal area; *LM*, left motor area; *RM*, right motor area; *LO*, left occipital area; *RO*, right occipital area.

EKG indicates the electrocardiogram, with electrodes placed on the right and left sides of the upper part of the chest.

The upright marker is equivalent to 50 microvolts; the horizontal marker to one second.

The first arrow marks, the beginning of stimulation of the carotid sinus; the second arrow, the end of stimulation, and the third arrow, the onset of convulsions. Immediately after beginning of stimulation, heart arrest occurred; about eight and one-half to nine seconds after stimulation high voltage slow waves arose from all cortical areas and at about eleven seconds tonic-clonic convulsions occurred, lasting about five seconds.

signs, just enough to demonstrate the presence of the reflex. The other 7 subjects, however, reacted on stimulation of the carotid sinus with tonic-clonic convulsions and loss of consciousness, and both the electroencephalogram and the electrocardiogram recorded abnormal responses. The history of each of these 7 volunteers revealed a preexisting pathologic condition, such as fainting spells and emotional instability. It was not surprising, therefore, to find a high incidence of positive carotid sinus reactions in a group of hospital patients with various mental diseases and a history of previous insulin, metrazol or electric shock treatment (table 5). Patients who had received shock treatment had a higher incidence of positive sinus responses than did untreated patients (table 5).

Table 5 shows that shock treatment enhances the effect of stimulation of the carotid sinus on both the control group of hospital patients and the patients who had undergone prefrontal lobotomy. The incidence

TABLE 5.—*Influence of Shock Treatment on Carotid Sinus Reflex*

	Hospital Patients (No Operation)		Patients After Lobotomy	
	Without Shock	With Shock	Without Shock	With Shock
Number of patients.....	19	21	9	16
Electrocardiogram *.....	11 (57.8%)	14 (66.6%)	6 (66.6%)	15 (93.7%)
+ - + +.....	6 (31.5%)	10 (47.6%)	3 (33.3%)	8 (50%)
+++ - + + + +.....	5 (26.3%)	4 (19.0%)	3 (33.3%)	7 (43.7%)
Electroencephalogram †.....	6 (31.5%)	14 (66.6%)	7 (77.7%)	16 (100%)
Convulsions.....	5 (26.3%)	12 (57.1%)	7 (77.7%)	15 (93.7%)

* + - + + indicates slowing of the heart (increased QRS interval); +++ - + + + +, heart arrest.

† Figures indicate the incidence of high voltage slow waves in the electroencephalogram.

of a positive effect of stimulation of the carotid sinus in patients with mental disease and previous shock treatment was similar to that of patients with prefrontal lobotomy but without previous shock treatment. On the other hand, the combination of shock treatment and lobotomy brought up the incidence of positive carotid sinus reactions to almost 100 per cent, as indicated by convulsions and changes in the electrocardiogram and the electroencephalogram.

COMMENT

It has been demonstrated by many authors that the effects of stimulation of the carotid sinus are primarily parasympathetic. The observation that positive carotid sinus reactions were present in almost all the patients with prefrontal lobotomy leads to the conclusion that section of the frontal lobes liberates the parasympathetic, or cholinergic, system from cortical inhibitory influences, at least to some degree. The pharmacologic examination of the autonomic nervous system with epinephrine

uncovered a response of the sympathetic, or adrenergic, system which was similar to the effect of stimulation with epinephrine after vagal block. However, vagal block could not possibly have existed, since the overactive carotid sinus reflex indicated a greater excitability of the vagus system. This increased excitability of the vagus system pointed to liberation from cortical-autonomic-vagal inhibition. If this conclusion is correct, it must be assumed that there are in the frontal lobe cortical-vagal inhibitory centers.

The overreaction of the adrenergic system in patients undergoing lobotomy to direct stimulation with epinephrine indicates that the sympathetic system, too, is liberated from cortical inhibitory centers. This view is further substantiated by the clinical observation of outbursts of rage in some patients after section of the frontal lobe. These outbursts of rage resemble the phenomenon of sham rage in cats, inasmuch as they are associated with signs of excessive autonomic function which seem chiefly sympathetic in nature.

The question arises whether the overreaction of the sympathetic or of the parasympathetic nervous system is due to loss of inhibitory cortical control or to liberation of the one system from the counteraction of the other. On the basis of ingenious ablation experiments on cats, in which removal of the cortical representation of the autonomic system resulted in dramatic overreaction of the adrenergic system with the manifestation of the syndrome of "sham rage," Kennard⁶ suggested that with the ablation of the frontal lobes the control of predominantly corticovagal centers was eliminated. However, in the monkey ablation of the frontal lobes does not lead to sham rage although similar signs of release of autonomic functions are observed. The predominance of adrenergic signs and the absence of observations on cholinergic signs in Kennard's experiments do not exclude the hypothesis that both the sympathetic and the parasympathetic nervous system are liberated from cortical inhibitory control. The absence of direct stimulation of the cholinergic system in Kennard's experiments complicates a comparison of her results with our observations on man. On direct stimulation, we found in man overreaction of both the sympathetic and the parasympathetic system, and, therefore, we arrived at the conclusion that this overreaction is due essentially to the loss of "cortical inhibition" of both the sympathetic and the parasympathetic system. This conception is in harmony with an opinion expressed by Langworthy⁷ and associates that "the cortical function is one of control or regulation of the finer autonomic adjustments and that its absence removes 'inhibition' and results in over-reaction of spasticity."

7. Langworthy, O. R.: Behavior Disturbances Related to Decomposition of Reflex Activity Caused by Cerebral Injury: An Experimental Study of the Cat, *J. Neuropath. & Exper. Neurol.* 3:87, 1944; cited by Kennard.⁶

Reitman⁵ suggested that in leukotomized patients there exists an increased resistance to drugs which upset the "autonomic equilibrium." Our observations, on the contrary, indicate a decreased resistance, or, in other words, an increased responsiveness of the autonomic nervous system to epinephrine, as well as other autonomic drugs which we have tested in a number of preliminary experiments.

Clinical observations, particularly with regard to the blood pressure, which will be reported in a separate paper, are strongly indicative that excitatory cortical-autonomic centers are also located in the frontal lobes. This is substantiated by reports in the literature. Since section of the frontal lobes interferes, of course, with the functioning of the cortical inhibitory, as well as excitatory, autonomic centers and their regulating influence on the autonomic nervous system, and since the patients show autonomic equilibrium postoperatively, it can be assumed that homeostasis establishes itself on a different level.

SUMMARY

The autonomic nervous system was examined in a control group and in a series of patients who had undergone prefrontal lobotomy. The sympathetic nervous system was tested pharmacologically with intravenous injection of 0.05 mg. of epinephrine hydrochloride (1:1,000). The parasympathetic system was examined by means of stimulation of the carotid sinus reflex. The effects were recorded with the electrocardiograph and the electroencephalograph, and the clinical manifestations were carefully noted.

Subcortical section of the frontal lobes interferes with inhibitory and excitatory autonomic centers in the cortex, resulting in overreaction of the autonomic nervous system to direct stimulation.

After frontal lobotomy autonomic equilibrium is eventually established at a new level and is brought about by readjustments of the autonomic system.

This work confirms other reports that cortical representations of the autonomic nervous system are located in the prefrontal area.

479 Commonwealth Avenue.

HYPERHIDROSIS

Study of a Case

ALICE J. PALMER, M.B.

SYDNEY, AUSTRALIA

ALMOST a century has passed since Claude Bernard,¹ in 1852, noted the vasodilatation which follows section of the sympathetic nerve supply to the side of the head. Ten years later, in 1862, Maurice Raynaud² described the disease of the extremities which has since borne his name. Since that time knowledge of the sympathetic nervous system, in both its normal and its abnormal state, has increased to the point where dysfunction not only can be recognized but can be treated and cured by sympathectomy.

There follows an account of the history, study and treatment of a patient exhibiting an abnormality of the sympathetic nerve supply to the extremities.

REPORT OF CASE

CLINICAL OBSERVATIONS

History.—A girl aged 18 years presented the symptoms of excessive sweating of her hands and feet, swelling of the fingers and blueness and coldness of all four extremities. The hyperhidrosis, which was the patient's chief complaint, had been present since childhood but had become definitely worse in the last four years. Droplets of sweat were left on the keyboard when she played the piano; writing at school examinations was made difficult by her wet hands, and the disability greatly interfered with her occupation as a trainee nurse. She stated that the hyperhidrosis was confined to the palms and soles, the amount of sweating from the rest of the body seeming to her quite normal. She had noticed that heat and emotional stress greatly accentuated her symptoms. The blueness and coldness of the fingers and toes had also been present since childhood. From the age of 12 she had had increasingly severe attacks of chilblains each winter. At first the accompanying swelling, blueness and coldness of the fingers disappeared with the onset of warmer weather, but for the last four years this return to normal had not occurred. The swelling was not present at all times; it was increased by any form of physical exertion or any extreme of temperature, either heat or cold. The hands were blue and cold at temperatures at which normal hands are warm and pink. Except for an increase in weight and mild mental lethargy, the patient

From the Department of Medicine, University of Sidney.

1. Bernard, C.: Sur les effets de la section de la portion céphalique du grand sympathique, *Compt. rend. Soc. de biol.* 25:168, 1852.

2. Raynaud, A. G. M.: De l'asphyxie locale et de la gangrène symétrique des extrémités, Paris, Rignoux, 1862, p. 177.

complained of no other symptoms. Her previous health record and her family history contained nothing relevant.

Examination.—The patient's general appearance was that of a normal adolescent girl. It was her hands which immediately arrested attention—droplets of sweat were literally dripping from the tips of her fingers. Moisture was present generally over the palms but was not perceptible on the dorsal surface. There was swelling of all the soft tissues from the wrist downward, particularly around the base of the fingers, which were firm and indurated on palpation. Over this area of greatest swelling the skin was a mottled purplish blue (fig. 1). The finger tips and the dorsum of the hands were bright pink. The hands were uniformly cold to the touch. The feet presented similar signs, though to a less extent. Other physical findings were normal, pulsation being present in the main arterial branches of the limbs.

Several features of this case precluded an outright diagnosis of Raynaud's disease, e.g., the severity of the hyperhidrosis and the presence of pronounced swelling. The cyanosis of the extremities was not definitely spasmodic, and there was never any associated pain. Accordingly, it was decided to carry out investigations to determine, if possible, the site of the abnormality causing the dysfunction of blood vessels and sweat glands and also to test possible therapeutic measures.

INVESTIGATIONS

Basal Water Loss.—EXPERIMENT 1.—Certain factors were known to produce hyperhidrosis, but the first question to be answered was whether excessive sweating occurred in the absence of specific stimuli. That is, was the basal activity of the sweat glands greater than normal? Also, of the body's total water loss under basal conditions, was an abnormal proportion contributed by the sweat glands of the palms and soles?

The continuous basal water loss from the body, the insensible perspiration, occurs at a constant rate for any one person and bears a relation to the basal metabolic rate. The normal loss varies from 17 to 21 Gm. per square meter of body surface per hour, with an average of 19.5 Gm. per square meter per hour.³ The lungs and the skin are the sources of this loss of water, the loss through the skin being by the physical process of transpiration and the physiologic process of sweating.⁴ Under controlled conditions of temperature and humidity, the insensible perspiration rate can be measured by the use of the sensitive Sauter balance. To answer the questions postulated in this experiment, the patient's insensible perspiration rate was measured in this way, the patient being in the basal state. The hands were then covered with rubber gloves and the feet with thick cotton socks to prevent evaporation. (Incidentally, this did not prevent sweating from the palms and soles, an important point, since a compensatory increase of water loss from the lungs would then have occurred.⁵)

Results: The insensible perspiration rate with the hands and feet uncovered was 15 Gm., and the insensible perspiration rate with the hands and feet covered was 14.8 Gm., per square meter per hour. These results indicate that the total

3. Lippmann, A.: On the Insensible Perspiration and Its Clinical Significance, M. J. Australia 1:569, 1942.

4. Kuno, Y.: Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934, p. 48.

5. Kuno,⁴ pp. 53-55.

rate of water loss for the patient under basal conditions was certainly not excessive—in fact, it was less than normal. As to the proportional amount lost by sweating from the palms and soles, this, also, was not greater than normal.

Since, then, it was concluded that specific stimuli were necessary in order to produce the hyperhidrosis of which the patient complained, the next step was to investigate the effects of applying such stimuli.

At this stage some means of detecting the presence of sweat other than with the naked eye became necessary. The method chosen was that described by Minor,⁶ which depends on the production of a colored compound from starch and iodine in the presence of moisture. A mixture composed of iodine, dilute alcohol and castor oil was painted on the skin, and over this was sprayed finely ground, thoroughly dried potato starch. In the presence of any moisture the grains of starch powder changed in color from white to a deep purple, a change which was readily discernible to the naked eye and to the camera.

Effects of Raising the Room Temperature

Room Temperature, C.	Mean Cutaneous Temperature of Hands, C.		Color of Hands		Sweating Reactions	
	Patient	Control	Patient	Control	Patient	Control
16 to 18	29.3 (84.7 F.)	34.0 (93.2 F.)	Purplish blue	Normal faint pink	None	None
19 to 21	30.0 (86.0 F.)	34.0	Purplish blue	Normal faint pink	None	None
21 to 23	30.3 (86.5 F.)	34.0	Purplish blue	Normal faint pink	None	None
23 to 25	30.7 (87.2 F.)	36.0 (96.8 F.)	Purplish blue	Normal faint pink	Small amount	None
25 to 28	30.8 (87.4 F.)	36.0	Purplish blue	Normal faint pink	Slight increase	None
28 to 30	30.8	36.0	Purplish blue	Normal faint pink	Moderate but not excessive	Small amount

Temperature readings of the skin were also required, and for this a sensitive dermotherm was used.

Heat and mental or emotional stress were the two most potent sudorific stimuli of which the patient complained; so the following experiments were carried out:

Effect of Heat.—EXPERIMENT 2.—The relative humidity being kept constant at 65 per cent, the room temperature was gradually raised from 16 to 30 C. The effects of this moderate increase in room temperature on the blood vessels and the sweat glands of the patient's hands were compared with those of a normal control.

EXPERIMENT 3.—The feet were immersed in a hot water bath at 48 C., and the effect on color and moisture of the hands was observed.

EXPERIMENT 4.—The hands were immersed in hot water at 48 C. to determine the effect of direct heat on the color and contour.

In experiment 2, the effect of raising the room temperature from 16 to 30 C. may be seen in the accompanying table. It will be noted that sweating commenced on the patient's hands at a room temperature of 23 C., as compared with 30 C.

6. Minor, V.: Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, Deutsche Ztschr. f. Nervenhe. **101**:302, 1928.

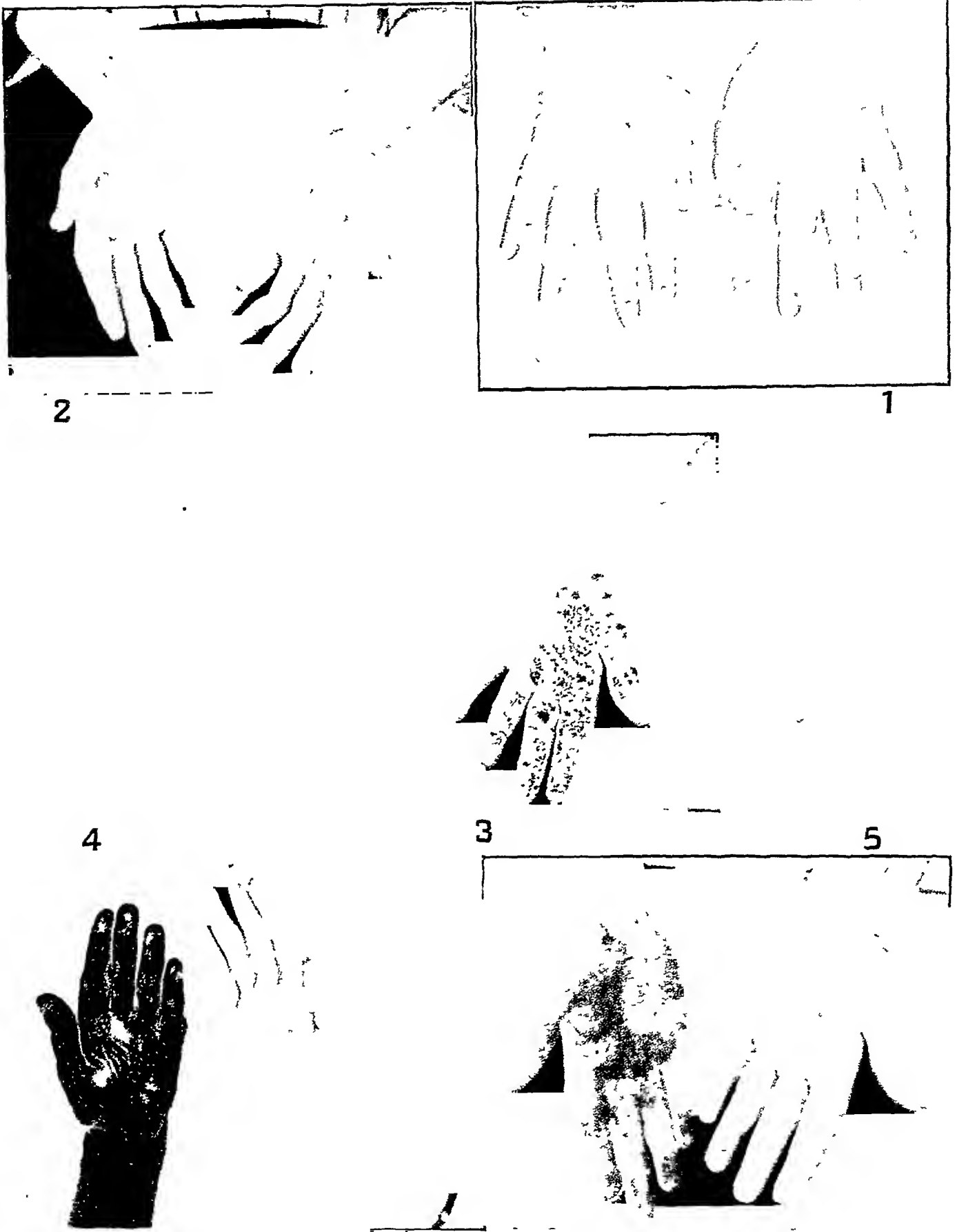


Fig. 1.—Hands before operation, showing bluish color and swelling around the proximal phalanges.
 Fig. 2.—Inhibition of sweating over the area supplied by the ulnar nerve after blocking of the nerve.
 Fig. 3.—Appearance of the left hand twenty-four hours after the first sympathectomy.
 Fig. 4.—Appearance of the hands twenty-four hours after the second sympathectomy.
 Fig. 5.—Absence of effect of mental stress on the sweat glands of the hands two years after operation.



for a normal control. The amount of sweating was also excessive. There was no significant rise in the cutaneous temperature of the patient's hands consequent on a rise of 14 C. in room temperature. At 30 C. the patient's hands were colder than those of the control at 16 C. Furthermore, the color of the hands remained purplish blue throughout the experiment.

In experiment 3, the hands were blue at the commencement of the experiment. During the next ten minutes the color gradually changed to a dull pink. The amount of sweating was sufficient to turn the starch to a confluent black layer.

In experiment 4, immediately the hands were placed in the hot water they turned bright pink, and the tissues around the proximal phalanges became greatly swollen. The sweating in experiments 2 and 3 was confined to the palms, there being no sweating perceptible on the dorsum.

Analysis of the results of these experiments reveals certain notable points in relation to the effect of heat on the blood vessels and sweat glands in this patient.

1. Vasoconstriction at low temperatures was more pronounced than in the normal hand. Moreover, it persisted up to rather high room temperatures. In contrast to this exaggerated vasoconstriction, the response to the direct heat of the water bath was an excessive vasodilatation. Thus, it would seem that adequate control of the peripheral vessels was lacking, but whether this was a local defect or whether the fault was in the nerve supply had still to be determined.

2. The response of the sweat glands to a rise in room temperature was precocious, occurring at lower temperatures of both room and skin than in the normal control. The distribution of the sweating was unusual, since in the normal person heat sweating occurs on the dorsum rather than the palm of the hand.⁷ Finally, the degree of vasodilatation and the activity of the sweat glands did not run parallel with one another; the one was delayed, whereas the other was precocious.

Effect of Mental Stress.—EXPERIMENT 5.—The patient was seated in a quiet, cool room alone with the observer. She was plied with problems in mental arithmetic. Sweating commenced on the palms within two minutes and rapidly increased to an excessive amount as compared with that in a normal person tested under the same conditions. It was interesting to note that there was no hyperhidrosis in the axillary region, which is a normal site for mental sweating.

Effect of Sudorific Drugs.—EXPERIMENTS 6 AND 7.—To complete the study of the effects of sudorific stimuli, it now remained to administer the two drugs, pilocarpine nitrate (experiment 6) and methylcholine chloride U.S.P. (acetyl-beta-methylcholine chloride; "mecholy chloride") (experiment 7). In each case the dose was 10 mg., given hypodermically. The effect of the drugs, not only on localized areas of sweat glands but on the total water loss from the body, was studied. The latter was done by use of the Sauter balance, which measured the progressive loss of weight due to evaporation of water from the body surface. The same dose of pilocarpine nitrate was subsequently administered to a group of medical students as a guide to the total water loss to be expected in a normal person.

The results are best shown in graphic form (fig. 6). It will be seen that both the rate and the total amount of water loss from the patient were greater than in the normal controls, but not strikingly so. The normal controls varied widely among themselves. There was copious sweating from the patient's hands and feet, the starch being changed from white to a confluent blackness. Sweating

7. List, C. F., and Peel, M. M.: Sweat Secretion in Man, Arch. Neurol. & Psychiat. 39:1228 (June) 1938.

from the hands and feet of the normal controls, was somewhat less in amount. Therefore it seems that the greater total amount lost by the patient could be explained by the localized excessive sweating of the hands and feet, and there was no need to postulate a hypersensitivity of the whole sweating mechanism to sudorific drugs.

Peripheral Nerve Block.—Hitherto, all the experiments had been designed to effect a stimulation of the sweat glands. The next step was to seek means of inhibiting them, particularly with a view to forecasting the effect of sympathectomy.

EXPERIMENT 8.—The sympathetic fibers supplying the vessels and sweat glands of the hands are carried in the main peripheral nerves. Of these, the ulnar nerve is readily accessible at the elbow, offering a convenient site for anesthetization.

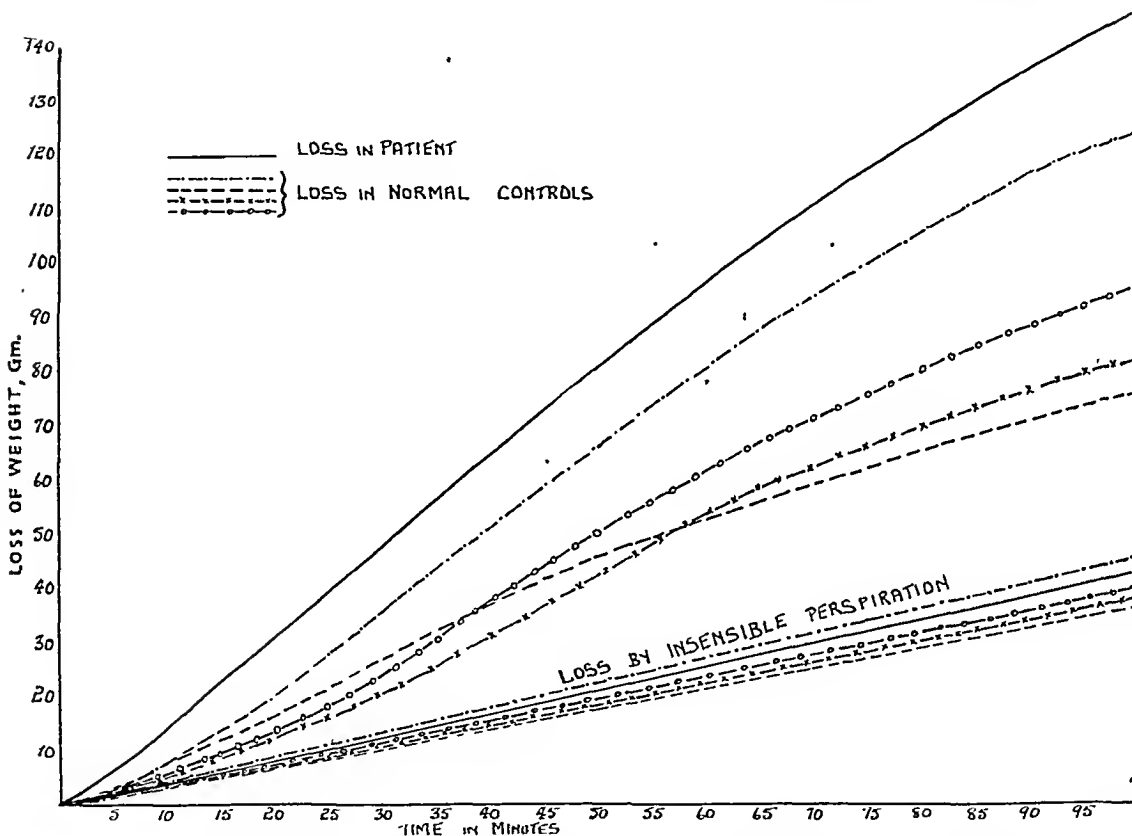


Fig. 6.—Patient's response to pilocarpine as compared with the response of normal subjects.

On two occasions 6 cc. of dibucaine ("nupercaine" or "percaine") hydrochloride with epinephrine hydrochloride was injected into the patient's right ulnar nerve, 1 cc. intraneurally and 5 cc. perineurally. On the first occasion sweating reactions were observed. The sweating was spontaneous, no additional sudorific stimulus being necessary. Less than ten minutes after the anesthetization, the right palm presented a striking picture, the effect resembling a textbook diagram of the distribution of the cutaneous nerves in the palm. A distinct line running down the center of the third finger and continuing across the palm divided the blackened, radial side from the white, ulnar side (fig. 2). The complete inhibition of sweating over the ulnar area lasted three hours.

The purpose of the second anesthetic was to study the vascular reactions and take readings of the cutaneous temperature. Vasodilatation was soon obvious over the ulnar area and persisted for several hours. An interesting phenomenon was seen on the radial side of the palm. For the first fifteen minutes the vessels remained constricted; then there was a gradual vasodilatation until the cutaneous temperature was finally as high as that on the ulnar side. The left hand, meanwhile, showed persistent vasoconstriction. The most likely explanation of this phenomenon seems to be the gradual diffusion from the ulnar to the radial side of the palm of some chemical vasodilatory substance. The results of this experiment are shown in figure 7.

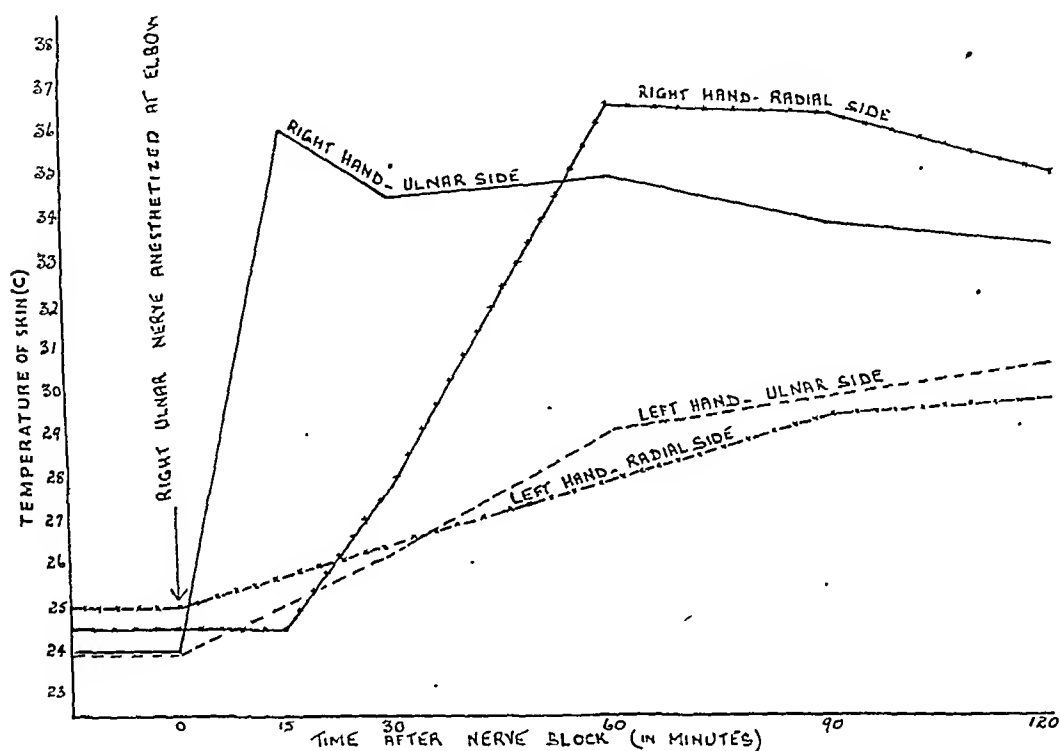


Fig. 7.—Effect of ulnar nerve block on the cutaneous temperature of the hand. Each point plotted on the graph is the mean of readings from eight specified points on the palm and the dorsum of the hand.

SYMPATHECTOMY

When the ulnar nerve block proved to be effective in relieving the patient's symptoms, sympathectomy was indicated as a more permanent form of treatment. The preganglionic type of operation was performed, the dorsal sympathetic chain being severed between the third and the fourth thoracic ganglia, first on the right side and three weeks later on the left. A lumbar sympathectomy for the relief of symptoms in the feet was not considered necessary, as these were of a much milder nature.

Postoperative Studies.—Twenty-four hours after the first operation, the treated (right) hand was warm, dry and pink. The untreated (left) hand was cold, dripping sweat and blue in color. The result of applying iodine and starch at this time may be seen in figure 3. The average difference in temperature between the two hands was 8 degrees (C.) [14.4 degrees (F.)]. Similar observations were made three weeks later, i. e., twenty-four hours after the second sympathectomy.

tomy and then on the fifteenth and thirtieth days of the postoperative period. The average temperature on each of these occasions is shown in figure 8. It is significant to note the slight fall by the fifteenth day, followed by a return to the immediate postoperative level by the thirtieth day. As to the sweating reactions, twenty-four hours after the second operation the left hand was completely dry, but a small amount of sweating was present on the palm of the right hand (fig. 4). On the fifteenth and thirtieth postoperative days both hands gave a slightly positive reaction to the iodine and starch test.

Effect of Heat, Mental Stress and Pilocarpine.—It was obvious that the patient's symptoms had been greatly alleviated by the sympathectomy, at least while she remained at rest. What would, now, be the effect of heat, mental stress and sudorific drugs?

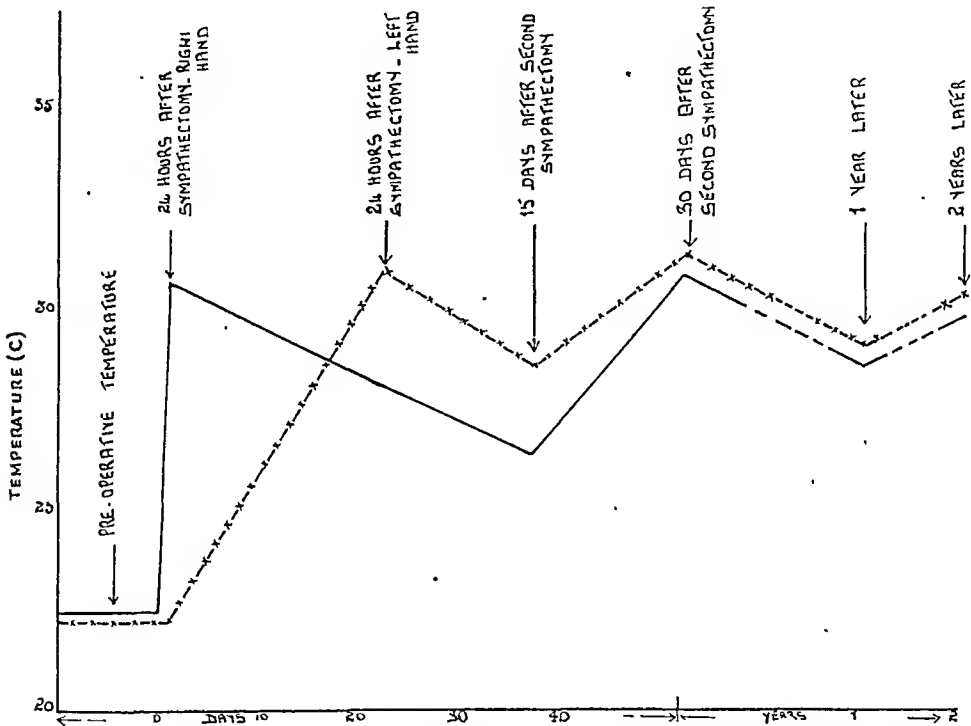


Fig. 8.—Changes in mean temperatures of the hands after sympathectomy. Values for the right hand are indicated by the solid line; values for the left hand, by the line of crosses and dashes.

To answer these questions, experiments 3, 5 and 6 were repeated in the fifth week of the postoperative period. Immersing the feet in water heated to 48 C. resulted in a rise of 3 degrees (C.) [5.4 degrees (F.)] in the average temperature of the hands. There was some sweating—enough to cause a patchy color change in the layer of starch, but a very small amount as compared with the confluent blackness of the preoperative experiment. Similarly, mental stress caused a much diminished amount of sweat to appear on the palms. When 10 mg. of pilocarpine nitrate was injected, the sweating of the palms was as copious as in the preoperative experiment.

Later Result of Operation.—Two years have passed since the sympathectomy was performed; so when the patient was seen recently, it was possible to gain

some indication of whether the immediate postoperative relief from her symptoms was to be only temporary or whether it was likely to be of a more permanent nature. It was found that the condition of her hands had improved even further. Despite its being midwinter, they were pink and quite dry and warm, their average temperature being 2 degrees (C.) [3.6 degrees (F.)] higher than that of a normal control. Swelling around the proximal phalanges had diminished but was still noticeable. Heat sweating and mental sweating were within normal limits. A final experiment was performed.

EXPERIMENT 9.—The right ulnar nerve was anesthetized at the elbow, and cutaneous temperatures and sweating reactions were observed. It was found that no rise of temperature occurred over the anesthetized area; i. e., there was no further vasodilatation. No sweating was visible on any part of the hands. Ten milligrams of pilocarpine nitrate was then injected hypodermically into the left arm. Within two minutes copious sweating broke out on the face and trunk. In contrast to the previous two occasions on which pilocarpine had been administered, only a minimal amount of sweating appeared on the hands, hardly more than could be accounted for by the stress of the injections and the heat of the photographic lamps. There was no difference between the anesthetized right ulnar area and the rest of the hands.

COMMENT

The purpose of the investigation in this case was to determine, if possible, the underlying cause and nature of the malady and to forecast the benefit likely to accrue from sympathectomy.

First, what was the site of the lesion? There were several possibilities—a local defect in the blood vessels and sweat glands or a defect in the sympathetic nervous system, either in its peripheral portion or centrally, as in the hypothalamus or the premotor cortex. A local fault seems the least likely explanation. Lewis⁸ brought forward much evidence in favor of a local hypersensitivity to cold being the basis of symptoms in Raynaud's disease. This might explain the vascular phenomena in the present case but would not explain the hyperhidrosis which was such a prominent feature. Also, a local defect would not account for the effectiveness of the sympathectomy in relieving the symptoms.

The control of vasomotor tone and the control of sweat gland activity are both functions of the sympathetic nervous system, and it seems likely that the fault lay either in the peripheral or in the central portion of this system. The theory of a postganglionic site as the origin of the hyperactivity is discredited by the success of the preganglionic operation. The theory of a central origin is supported by several points—the symmetric distribution of the symptoms, the involvement of all four limbs and the response to reflex stimuli, such

8. Lewis, T.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers: A Variety of Raynaud's Disease, *Heart* 15:7, 1929.

as that of the hands to heating of another portion of the body. The potent effect of psychic stimuli in provoking the symptoms, as well as the tendency to obesity which became manifest concurrently with the increase in severity of the sweating and vascular symptoms, suggests a central disorder. Whether the premotor cortex or the hypothalamus was primarily at fault it is not possible to say. The sweating disturbance in this case is similar to that described by Adson, Craig and Brown in their cases of "essential hyperhidrosis."⁹

The next question to be decided is whether the defect was purely functional or whether the symptoms could have resulted from an organic lesion. The latter seemed quite possible at one stage, for in the attempt to expose the dorsal portion of the sympathetic chain in the first operation an abnormally dense plexus of veins was observed closely surrounding it. Could pressure from this plexus be the cause of the patient's symptoms? The answer to this question was in the negative, because the symptoms were bilateral and the second operation revealed no abnormal venous plexus on the other side. No evidence of any other organic lesion was seen; so one must conclude that the derangement was one of function, and not of structure. What caused the localized dysfunction is obscure. There was no history of infection, such as encephalitis, no trauma or nutritional disease and nothing in the family history to suggest a genetic factor. A congenital anomaly of the sympathetic nervous system is the only satisfactory explanation, and the fact that the symptoms dated from childhood lends weight to this theory.

During the investigations several observations were made which are worthy of note. The distribution of heat sweating on the hand was unusual. Instead of its being confined to the dorsum, leaving the palms relatively free, the palms sweated copiously, whereas no moisture was discernible on the dorsum.

The response to pilocarpine was interesting on the three occasions on which the drug was given. Before operation, and one month after sympathectomy, the drug stimulated the sweat glands of the hands to great activity. On the third occasion, two years later, the response was negligible and, moreover, was not affected by the ulnar nerve block. The site of action of pilocarpine is thought to be directly on the effector cells, and not on nerve fibers or nerve endings;¹⁰ so one

9. Adson, A. W.; Craig, W. McK., and Brown, G. E.: Essential Hyperhidrosis Cured by Sympathetic Ganglionectomy and Trunk Resection, *Arch. Surg.* **31**:794 (Nov.) 1935.

10. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, The Macmillan Company, 1941, p. 391.

would not expect sympathectomy to alter the response to the drug. If this theory of the site of action is correct, a possible explanation for the lack of response on the third occasion is that the sweat glands of the hands had atrophied as a result of interruption to the central connections of their nerve supply. This would be an atrophy due to disuse, not the atrophy resulting from cutting the immediate fibers supplying the glands, for these postganglionic fibers are left intact by the preganglionic operation. Such an explanation is not invalidated by the fact that the second occasion was also in the postoperative period, for it was then but a month after the operation and the sweat glands would not have atrophied sufficiently to prevent them from responding to a direct stimulus. Also, at this stage one would expect a strong, positive reaction to a parasympathomimetic drug such as pilocarpine because of the so-called sensitization phenomenon. This response was first noted in connection with the effect of epinephrine on the ear vessels of a rabbit after sympathectomy.¹¹ The nerve endings to the sweat glands are cholinergic and are therefore hypersensitive to parasympathomimetic drugs, although they are part of the sympathetic system. The postganglionic type of operation renders the patient much more liable to this sensitization phenomenon, and the preganglionic operation was designed to avoid it. Nevertheless, it still occurs, though to a much less extent.

The dramatic complete relief from symptoms for the first four to five days after operation and their gradual partial return for a limited period was not a unique phenomenon in this patient. It has often been observed to follow sympathectomy for peripheral vascular disorders.¹²

In conclusion, it seems from present indications that the patient has a fairly good chance of enjoying permanent relief from her symptoms. Two years after operation, there are no signs of nerve regeneration, and her hands are as warm, dry and pink as those of a normal person.

SUMMARY

A girl gave a history suggestive of Raynaud's syndrome but presenting unusual features.

11. Meltzer, S. J., and Meltzer, C.: The Share of the Central Vasomotor Innervation in the Vasoconstriction Caused by Intravenous Injection of Suprarenal Extract, *Am. J. Physiol.* 9:147, 1903; On the Effects of Subcutaneous Injection of the Extract of the Suprarenal Capsule upon the Blood Vessels of the Rabbit's Ear, *ibid.* 9:252, 1903.

12. White, J. C., and Smithwick, R. H.: *The Autonomic Nervous System*, London, The Macmillan Company, 1942, p. 174.

Investigations were carried out to study the effect of heat, mental stress, sudorific drugs and peripheral nerve block on the sweat glands and the blood vessels of the hands.

A preganglionic dorsal sympathectomy was performed.

The preoperative experiments were repeated, and the patient's symptoms were found to be greatly relieved.

The site and nature of the disorder and its etiologic factors are discussed, and mention is made of several interesting points observed during the investigations.

Prof. C. G. Lambie permitted the investigations on this patient, who was under his care. Dr. Ivor Hotten performed the peripheral nerve blocks, and Dr. A. Lippmann and Mr. M. J. Morrissey cooperated in several of the experiments. Dr. S. Woodward-Smith made the color photographs. The operation of sympathectomy was performed by Dr. Gilbert Phillips.

University of Sydney.

SPINAL EXTRADURAL CYST

Report of a Case, with Particular Reference to a Possible Diagnostic Aid

OSCAR A. TURNER, M.D.

YOUNGSTOWN, OHIO

THE INTEREST in noninflammatory and non-neoplastic cysts of the spinal extradural space was initiated by the report of Elsberg, Dyke and Brewer¹ in 1934. They described 4 cases of such a cyst encountered among 250 tumors of the spinal cord and evolved a clinical and roentgenologic syndrome which has proved to be diagnostic of the condition. They described the combination of signs and symptoms as follows:

The individual is an adolescent with the history of symptoms of a progressive spastic paraplegia. Pain is absent or is not a prominent symptom. The objective disturbances of sensibility are slight and their upper level is in the mid-thoracic dermatome. The manometric tests demonstrate a subarachnoid block with the characteristic spinal fluid changes of cord compression. Measurements on anteroposterior x-ray films show that the interpedicular spaces of three or more vertebrae are enlarged. The pedicles of the affected vertebrae, especially those of the sixth, seventh, and eighth, are narrowed and atrophic.

Cloward and Bucy,² in 1937, first recognized the association of the condition known as vertebral epiphysitis, or Scheuermann's disease,³ with the presence of spinal extradural cyst and thus added another component, kyphosis dorsalis juvenilis, to the syndrome described by Elsberg, Dyke and Brewer.¹ The literature pertaining to this cyst and the associated changes in the spinal column was reviewed by Adelstein⁴ in 1941, who reported an additional case, bringing the total recorded in the literature at that time to 17 cases. Since this review other cases have been described, and in table 1 are listed the cases reported since 1941. However, a case reported by Collins and

From the Neurosurgical Service and the Neuropathologic Laboratories of the Jewish Hospital of Brooklyn, Brooklyn.

1. Elsberg, C. A.; Dyke, C. G., and Brewer, E. D.: The Symptoms and Diagnosis of Extradural Cysts, *Bull. Neurol. Inst. New York* **3**:395-417, 1934.

2. Cloward, R. B., and Bucy, P. C.: Spinal Extradural Cysts and Kyphosis Dorsalis Juvenilis, *Am. J. Roentgenol.* **38**:681-706, 1937.

3. Scheuermann, H.: Kyphosis dorsalis juvenilis, *Ztschr. f. orthop. Chir.* **41**: 305-317, 1921.

4. Adelstein, L. J.: Spinal Extradural Cyst Associated with Kyphosis Dorsalis Juvenilis, *J. Bone & Joint Surg.* **23**:93-101, 1941.

Marks⁵ had not been previously included in the collective review on the subject but was noted by Hamby⁶ in his review of intraspinal tumors in childhood. It is to be noted that Mayfield and Grantham⁷

TABLE 1.—Cases of Extradural Cyst Reported Since 1941

Case No.; Date Reported	Author	Age	Duration of Symptoms	Sex; Race	Location of Cyst	Dilatation of Spinal Cord	Results and Comment
18 1915	Collins and Marks ⁵	15*	4 yr.	F W	T 3-6	?	Complete neurologic recovery; no opening into subarachnoid space
19 1939	Turnbull ¹¹	14	3 mo.	F W	T 8-10	Present	Complete recovery; patient treated for tuberculous on first admission; operation 4 yr. after onset of symptoms
20 1940	Meredith ^{15c}	41	8 mo.	M W	C 7, chiefly on right	?	Complete recovery; previous injury to cervical part of spine; possible traumatic origin
21 1942	Mayfield and Grantham ⁷	16	3 yr.	M W	T 6-9	None †	Complete recovery; symptoms followed injury; remission in symptoms for 1 yr.
22 1942	Mayfield and Grantham ⁷	26	12 yr.	M N	T (5) 6-8	Present† T 6-7	Practically complete recovery; history of 4 distinct remissions
23 1944	Good, C. A.; Adson, A. W., and Abbott, K. H.: <i>Am. J. Roentgenol.</i> 52: 53-60, 1944	42	8 yr.		T 8-L 1	Present†	Radiopaque oil demonstrated in cyst before and after removal
24 1945	Shenkln, H. A.; Horn, R. C., and Grant, F. C.: <i>Arch. Surg.</i> 51: 125-146, (Oct.) 1945	51	3 mo.	F	T 7-9	Present T 7-9	Complete recovery; tumor attached to T 9 root, measured 6 by 2.5 by 2.5 cm.; no cell lining layer
25	...	13	2 yr.	F	T 6-8	Present	Complete recovery; no attachment to surrounding structures; development of kyphosis post-operatively
26 1945	Cohen, I.: <i>J. Mt. Sinai Hosp.</i> 12: 116-118, 1945	48	3 mo.	F	T 8	Pedicle destroyed†	Results questionable; extradural neuroblastoma (sympathicoblastoma) at C 10 also present
27 1946	Turner	11	5 mo.	M W	T 10	Present†	Complete recovery

* Age at time of the first admission to the hospital.

† Dilatation as seen in the roentgenogram.

5. Collins, J., and Marks, H. E.: Early Diagnosis of Spinal Cord Tumors. *Am. J. M. Sc.* 149:103-112, 1915.

6. Hamby, N. B.: Tumors in the Spinal Canal in Childhood: An Analysis of the Literature with Report of a Case, *J. Nerv. & Ment. Dis.* 81:24-42, 1935.

7. Mayfield, F. H., and Grantham, E. G.: Spinal Extradural Cysts, Surgery 11:589-595, 1942.

did not consider the cases reported by Schlesinger⁸ and by Krause⁹ as verified instances of extradural cyst. A total of 27 cases have been reported up to the present time. This does not include the case of Blum,¹⁰ discovered in the literature by Cloward and Bucy² and noted by Mayfield and Grantham⁷ as probably being one of extradural cyst.

It is generally recognized that in the presence of a complete or an incomplete subarachnoid block due to an intraspinal tumor withdrawal of spinal fluid from the subarachnoid space below the lesion may result in aggravation of already existing symptoms or signs. In such instances, a partial block may become complete; motor power may be further diminished, and changes in sensibility may become more pronounced. This has been interpreted as due to further impaction of the tumor against the already compressed cord, and in unusual cases acute compression of the cord may occur. Such changes are prone to occur oftener in the presence of movable growths, such as the perineural fibroblastoma, than with a fixed or sessile tumor, such as the meningioma or the intramedullary glioma. More frequently, however, removal of spinal fluid from below the site of the tumor, or increase in pressure of the fluid above the tumor, such as occurs in the determination of the spinal fluid dynamics, is associated with little change in the symptoms or physical signs other than increase in pain in the distribution of the involved posterior nerve roots if such pain is already present. Improvement in the clinical picture is still more unusual, and in the case reported here there was striking improvement in the motor power of the paralyzed lower extremities after removal of spinal fluid. This has never previously been noted in connection with extradural cysts, although Turnbull¹¹ was able to demonstrate recurrence of symptoms with activity following improvement as a result of prolonged rest in bed.

REPORT OF CASE

History.—An 11 year old boy, of Italian parents, was admitted to the hospital on Jan. 29, 1941, with the complaint of progressive loss of motor power in both lower extremities over a period of five months. The family history was essentially noncontributory, and the patient was one of 7 children, the ages of the siblings ranging from 14 to 28 years. He had a normal spontaneous birth at full term, and the neonatal period had been uneventful. There was a history of pneumonia in infancy and of asthmatic attacks with respiratory embarrassment every two to

8. Schlesinger, H.: Beiträge zur Klinik der Rückenmarks-und Wirbeltumoren, Jena, Gustav Fisher, 1898, p. 46; cited by Adelstein.⁴

9. Krause, W. C.: A Case of Cyst Within the Spinal Canal, *Brain* 30:533, 1907; cited by Adelstein.⁴

10. Blum, W.: Rückenmarksläsion bei Scheuermann'scher Krankheit (Kyphosis dorsalis adolescentium), *Schweiz. med. Wchnschr.* 66:283-285, 1936.

11. Turnbull, F.: Spinal Extradural Cyst, *Canad. M. A. J.* 41:250-253, 1939.

three months since the age of 5 years. There was no history of rickets or dietary deficiency.

The child had been well until late in August 1940, at which time it was noted that he began to drag the legs in walking. About two weeks after this it was observed that he fell frequently. The difficulty in gait progressed to total incapacitation, and he had been confined to bed for a month prior to admission to the hospital. At the time of his admission voluntary movements of the lower extremities were reduced to a minimum, but he had not been aware of sensory changes or paresthesias. The rectal sphincter had not been affected, but for about a month there had been difficulty in starting the urinary stream.

Examination.—The boy was well developed and slightly obese and did not appear ill. There was spastic paraplegia, with only minimal voluntary movement present in the lower extremities. Occasional spontaneous flexor spasms were present, particularly after painful stimulation. There was well sustained ankle and patellar clonus bilaterally, associated with pronounced hyperreflexia of the lower extremities. Plantar stimulation resulted in an extensor toe response, stronger

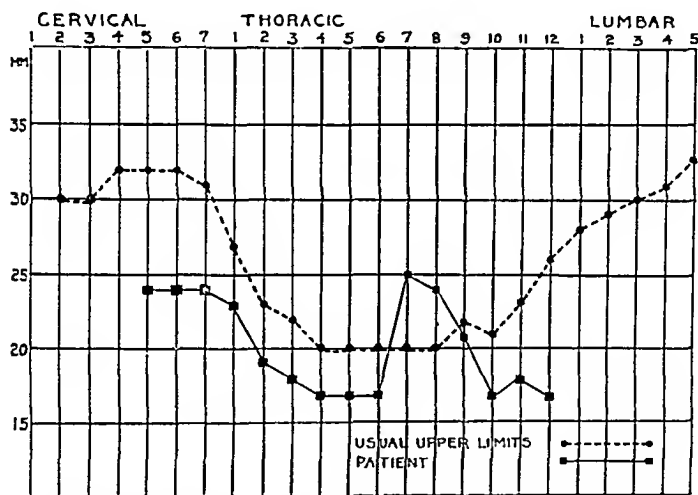


Fig. 1.—Graph showing the localized erosion of the pedicles of the seventh and eighth thoracic vertebrae. Normal measurements are from Elsberg and Dyke (Bull. Neurol. Inst. New York 3:359-394, 1934).

on the left side than on the right. The Gordon-Oppenheim sign was present bilaterally, and there was a strongly positive suprapubic adductor sign. The abdominal reflexes were absent, and there was a positive Beevor sign, with conspicuous upward deviation of the umbilicus on raising the head against resistance. Sensory examination disclosed a sharp sensory level at the ninth thoracic dermatome with a narrow band of hyperesthesia on the left. On the left side sensation was practically absent, while on the right side the sensory loss was less complete. The sensory defect was for all modalities, although the temperature sense was less involved than was the pain or touch sense. The loss of position and vibration sensation was complete. There was possibly less impairment of sensation over the scrotum than in the adjacent regions. No evidence of kyphosis or any other spinal deformity was present.

Roentgenographic examination of the thoracic portion of the spine revealed notable enlargement of the canal, chiefly in the region of the seventh and eighth thoracic vertebrae. There were erosion and atrophy of the pedicles, as well as

erosion of the posterior margins of the bodies of the affected vertebrae (fig. 1). Lumbar puncture revealed an initial pressure of 170 mm. of water, which dropped to 135 mm. after the removal of 1 cc. of spinal fluid. The application of pressure up to 80 mm. of mercury by means of a cuff around the neck caused no change in the intraspinal pressure, demonstrating the presence of a complete subarachnoid block. The first cubic centimeter of fluid removed was slightly xanthochromic, whereas the remainder was colorless. The release of 4 cc. of fluid reduced the intraspinal pressure to 45 mm. of water. The fluid contained 4 lymphocytes per cubic millimeter and 67 mg. of total protein per hundred cubic centimeters. Examination of the patient immediately after the withdrawal of spinal fluid disclosed no change in the sensory status, although there was striking improvement in the motor power of the lower extremities. An hour and a half later the patient was able to lift either leg completely off the bed, and he had more motor power in the legs than had been present for many months prior to hospitalization. No pain was associated with the withdrawal of the spinal fluid.

Operation.—Operation disclosed the presence of a large extradural cyst, which was completely exposed only after the laminas of the sixth to the eleventh thoracic

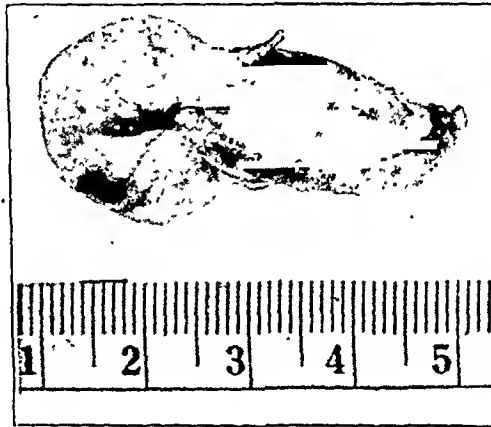


Fig. 2.—The intact cyst after removal at operation. The clip indicates site of the pedicle.

vertebrae had been removed. It was necessary to remove a portion of the articular facets to expose completely the lateral margins of the cyst. This was done so that a careful search could be made for extensions of the wall of the cyst along the nerve roots. The wall was thin and translucent; and, although it was adherent to the nerve roots, it could be demonstrated with certainty that no extensions were present. At the time of exposure, the cyst was rather tense, and, while aspiration of 10 cc. of clear, colorless fluid caused considerable relaxation of the wall of the cyst, fifteen minutes later the fluid had been replaced and the cyst had again become tense. Dissection of the cyst from the adherent structures exposed a pedicle 1 cm. in diameter which passed through a defect in the dura at one point about 5 mm. above the site of exit of the eighth thoracic root on the right side. It was certain that the cyst represented a herniation of the leptomeninges through the dural defect, and removal of the cyst by transection of the pedicle left an opening through which spinal fluid drained and the uncovered cord could be seen. The defect was closed with several interrupted silk sutures.

Postoperative Course.—Convalescence was uneventful, and progressive improvement followed removal of the cyst. At the time of discharge from the hospital

the patient was able to walk. Two weeks after operation perception of touch, pain and temperature had returned to normal, although there was still some impairment of vibration and position sense. To prevent the development of a spinal deformity, the patient was fitted with a body cast, which was later replaced with a form-fitting brace.

Pathologic Study.—The cyst measured 6 by 1.5 cm. The external surface was gray, smooth and glistening in some areas, while elsewhere it was roughened by yellowish gray tags of adherent tissue. In the central portion was an opening 8 mm. in diameter, at which point the pedicle had been attached. Loosely adherent to the pedicle side of the cyst were several moderate-sized vessels and a small segment of nerve root (fig. 2). The inner surface of the cyst was smooth, gray and dull, and without evidence of tumor nodule or gross inflammatory change.

Microscopically, the wall of the cyst was composed of a double layer of rather heavy collagenous tissue, which was partly hyalinized. An occasional flattened cell could be recognized on the inner surface. Between the inner and outer connective tissue layers forming the wall of the cyst was a layer of tissue formed either by a bank of cuboidal or flattened cells or by a mesh of elongated and stellate cells with interlacing processes. Sections of the nerve root and epidural fat were not unusual.

COMMENT

Several explanations have been offered to account for the origin of the spinal extradural cyst, and attention has centered generally on the suggestion of Elsberg, Dyke and Brewer¹ that it arises either as a congenital diverticulum of the dura mater or as a herniation of the arachnoid through a dural defect. No explanation has been offered, however, for the constant location of this cyst in the thoracic region. The suggestion that it is the result of herniation of the arachnoid has been favored by many authors, and there is much to support this view. Free communication between the cyst and the subarachnoid space was demonstrated by Mayfield and Spurling,¹² by Kelly¹³ and by Cloward and Bucy.² On the basis of the microscopic appearance of the cyst, the last-mentioned authors favored the theory of origin from a dural diverticulum, as did Robertson and Graham.¹⁴ In this respect, it is of interest that of the 27 cases reported in the literature to date, in only 3¹⁵ was there any significant history of trauma related to the occurrence of symptoms. In the case reported here, the evidence in favor of herniation of the arachnoid was quite definite, and a characteristic pedicle passing through a sharply delimited dural defect could

12. Mayfield, F. H., and Spurling, R. G., cited by Cloward and Bucy.²

13. Kelly, T. S. B.: Non-Parasitic Extradural Cyst of the Spinal Canal, *Lancet* 2:13-16, 1937.

14. Robertson, J. F., and Graham, C. P.: Spinal Extradural Cyst Associated with Kyphosis Dorsalis Juvenilis, *Ann. Surg.* 110:285-290, 1939.

15. (a) Mayfield and Grantham.⁷ (b) Mayfield and Spurling.¹² (c) Meredith, J. M.: Unusual Tumor and Tumor-Like Lesions of the Spinal Canal and Its Contents with Special Reference to Pitfalls in Diagnosis, *Virginia M. Monthly* 67:675-687, 1940.

be observed. Typically, the cyst is composed of avascular fibrous tissue, and in most instances epithelial cells or their remnants line the inner surface. In the case reported by Adelstein,⁴ however, the lining cells were absent. Cloward and Bucy² noted the resemblance of the lining cells to the cells of the arachnoid membrane.

Of the various explanations offered for the association of the condition known as *kyphosis dorsalis juvenilis* and the extradural cyst, that of Cloward and Bucy² appears to have the best anatomic and physiologic foundation. It has been repeatedly pointed out that the changes in the vertebrae are not of an inflammatory nature and do not predominantly or selectively involve the vertebral epiphyses. The term *vertebral epiphysitis* for the changes observed in the vertebrae is, therefore, not correct. These authors pointed out that in the loose areolar tissue of the epidural space there are many vascular channels, including the main venous drainage of the vertebral body. Drainage is by way of the large posterior central vein, which leaves the body of the vertebra at the center of its posterior surface, to be eventually drained by the intervertebral veins. This large central vein, which is joined by the anterior transverse and anterior longitudinal venous sinuses before emptying into the azygos system by the intercostal veins, is actually occluded by the pressure of the cyst, which is wedged between the bony wall of the canal and the dura mater. The changes in the vertebral bodies can, then, be explained on the basis of venous congestion and stasis within the body of the vertebra itself. The partial collapse of the contiguous vertebral bodies results in the rounded and fixed deformity, which is said to be self limiting and never severe, assuming an arrested state within a few months of the onset.

The improvement in the neurologic signs following removal of spinal fluid can be explained by the relaxation of tension in the cyst with lessened compression of the cord after removal of fluid from the cyst itself. It is probable that some relaxation of tension in the cyst also occurs through lengthening due to release of fluid from the subarachnoid space below the lesion, but the cyst wall appears to be relatively inelastic, and this factor is probably not a considerable one. Such a period of relief is likely to be followed within a relatively short time by returning signs of compression, due to replacement of the fluid removed from the cyst. This was demonstrated by the manner in which the cyst refilled with fluid after aspiration at the time of operation in the case described here. As has been emphasized by Cloward and Bucy,² it must be remembered that even in instances of complete obstruction of the subarachnoid space manometric rise on jugular compression may occur as a result of transmission of pressure, owing to the fluid content and cystic character of the tumor mass. Such transmission of pressure through a fluid-containing tumor of

the spinal canal has also been noted in certain vascular tumors. In such instances the presence of changes in the interpedicular spaces or myelographic studies will demonstrate the level, and in case of the latter, the presence, of a subarachnoid block.

Further light on the character of the fluid contained in the cyst and on the presence of free communication between the spinal subarachnoid space and the cyst may be had from a comparison of the chemical constituents of the fluid removed separately from the two spaces at the time of operation. Reference to table 2 indicates the

TABLE 2.—*Comparison of Spinal Fluid and Cystic Fluid Removed at Operation*

	Spinal Fluid	Cystic Fluid
Total nitrogen, mg./100 cc.....	316.0	319.0
Potassium, mg./100 cc.....	11.1	13.1
Calcium, mg./100 cc.....	5.8	5.8

presence of similar or identical amounts of potassium, calcium and total nitrogen in the two fluids. The difference in the amount of potassium is explained by the contamination of the fluid from the cyst with a very small amount of blood at the time of removal.

SUMMARY

1. A case of extradural spinal cyst associated with early roentgenologic manifestations of kyphosis dorsalis juvenilis and erosion of the pedicles is reported.

2. A possible diagnostic aid, consisting of clinical improvement following removal of spinal fluid with subsequent recurrence of compression of the cord, is presented.

3. Further clinical and anatomic evidence of the origin of the cyst as a herniation of the pia-arachnoid through the dura is given.

4. Chemical studies showing the similar or identical character of the fluid in the cyst and in the subarachnoid space are presented.

226 North Phelps Street.

Case Reports

PSYCHONEUROTIC REACTION TO MULTIPLE PSYCHOSES AMONG SIBLINGS

FRED FELDMAN, M.D.*

Instructor in the Department of Neurology and Psychiatry, Albany Medical College
NEW YORK

THE CONCURRENCE of mental illness in two or more members of the same family has long posed a problem of concern to psychiatry. In an older era, this problem was investigated almost exclusively from the point of view of the psychoses. Studies of heredity and of folie à deux best exemplify this older vantage point. More recently, the intrafamily conflicts giving birth to the psychoneuroses have emerged into the sunlight of objective inquiry. Psychoses and psychoneuroses have rarely been considered together, however. This paper reports a family of which at least 4, and perhaps 6, members were psychotic and stresses the effect of this knowledge in causing a psychoneurosis in another sibling, a soldier. The relation of psychoses and psychoneuroses is discussed from the standpoint of nomenclature, traditions and basic conceptions.

REPORT OF A CASE

A soldier aged 28 was admitted to the psychiatric division of a convalescent hospital in April 1946, complaining of headaches and easy fatigability. The family history was notable in that the paternal grandmother died in a psychiatric hospital. The diagnosis was probably senile dementia, since the patient remembered that she had first been hospitalized in her eighties. A paternal uncle was also mentally ill for many years, was hospitalized several times and was described by the patient as "very wild—he was always escaping from institutions." The mother and father were described as nervous but otherwise well; apparently, the father, a shipyard worker, was able to maintain the family at a marginal or somewhat better economic level. The patient stated that his father had always seemed more antagonistic toward him than toward the other children, and he recalled a dramatic incident when he was 10 or 12 in which he knocked his father down and out. He described his father as a steady worker, but "a man whose temper seems to dominate him. I think he's a sick man, too." The relationship to the mother, a somewhat passive woman, was apparently not close. The parents were frequently in conflict, but never to the point of separation. The patient recalled frequent quarrels in the home and much protecting of the children on the part of the mother against the temper tantrums of the father. On the whole, he remembered the home as one in which some degree of affection was manifested by both parents toward all the children during their formative years.

The patient had 11 siblings, 5 brothers and 6 sisters. Three sisters and 1 brother had been hospitalized with verified diagnoses of schizophrenia. One pair of twin sisters were hospitalized within six months of each other, at the age of 19; they were interned for a period of six months, in 1 case, and of twelve months,

* Formerly Captain Medical Corps, Army of the United States.

in the other, and had been released within the year prior to the patient's hospitalization. The patient stated that so far as he knew their adjustment was adequate except that one of the twins "talks all the time." The third of the schizophrenic sisters was first hospitalized at the age of 28, for one year; at the time of my interview with the patient she was 34 and living with her husband, but the patient said that "she doesn't sound right to me." The fourth schizophrenic sibling, a brother, was hospitalized at the age of 28 for about one year, had recently been discharged and was unemployed. Among the other 5 siblings were twin brothers, about whom the patient knew little except that they were both hospitalized at the age of 7. He expressed the opinion that one of the twins was never sick but was hospitalized only "because it was impossible for the family to take care of him." He was released at the age of 10 and subsequently made a fair adjustment. The other twin was still institutionalized, but the patient could not recall where and did not know the cause. Mental deficiency may perhaps be considered.

The patient was born and raised in New York city; he described himself in childhood as "nervous and easily upset." He was frequently truant from school, although attending "adjustment classes" until the age of 16. He was considered delinquent during adolescence and was twice arrested, once for forgery of a government check and once for stealing 28 cents out of a cash register. A suspended sentence was obtained on each occasion. After leaving school, however, he began to work and showed an increasingly better vocational adjustment, leaving a job only to improve himself and eventually earning about \$50 a week as helper to a truck driver. He enjoyed the work chiefly because he was successful at it. He was married at 21, to a girl of 19, whom he described as a "good housewife and manager," and there followed a period of compatible emotional and sexual adjustment, during which 2 children were born.

The patient came into psychiatric channels while overseas, through the recommendation of the War Department, acting on the basis of a letter sent by the patient's mother. The latter wrote she had noted that the few times that she saw him "he was very much depressed and was unhappy." She indicated that the patient had always "worried a great deal" about the siblings who had been ill and that at the time of his induction he was ashamed to reveal the family history to the draft board. His feelings about induction had been mixed, since he desired to prove his capacities to himself and yet was reluctant to leave his wife and children. He was in service for several months in this country, adjusting satisfactorily, and was transferred overseas late in 1945. At the time he was first called in by the psychiatrist, he indicated that he had been aware of increasing tension since going overseas. His sleep was restless and broken by disturbing dreams. He vomited frequently, noted dizzy spells, found it difficult to concentrate and felt that his memory was impaired. Symptoms of this nature had never troubled him before, nor had he ever previously been aware of periods of depression, which now became frequent. The psychiatrist felt that the degree of anxiety and depression was sufficient to warrant hospitalization and evacuation to the United States.

On admission to the convalescent hospital in this country, the patient's status seemed somewhat improved. He related well to the therapist and displayed considerable insight. Although he reiterated the surface symptoms already itemized, he said spontaneously, "It's really my worry about what happened to all my brothers and sisters." He had always been concerned about the possibility of illness suddenly appearing in himself, and after the birth of his children his apprehension mounted. His fears were nourished by the anxiety of his wife, who began

to brood over the foredoom which threatened her children. The patient had on many occasions found it necessary to reassure her on grounds where he did not stand too firmly himself. The unbridgeable absence from her while he was overseas heightened his uncertainties about himself, his children and his wife's devotion. He was still mildly depressed and gave evidence of a passive, dependent, insecure personality, but nevertheless showed good achievement drive. Psychotherapy was carried on for three weeks at the level of reassurance and ventilation, with some interpretation concerning problems of inheritance of mental illness. On discharge, he was considerably improved and was urged to seek further psychiatric contacts for himself and his wife in civilian life.

Instances of four or more psychotic members in one sibship are so infrequently encountered that reports in the literature are still seen only semioccasionally. A survey of the literature of the past ten years revealed less than a score of recorded cases, most of them chronicled as examples of *folie à deux*, and several others illustrating the inheritance of mental illness. In only two papers are psychoneuroses mentioned, and in those only briefly and tangentially. Grover (1937), in a study of *folie à deux*, suggested that schizophrenic reactions and hysteria are related, since either may be precipitated by suggestion, although the delusions of hysteria are surrendered more easily than those of schizophrenia. Osborn (1945) reported on 5 psychotic sisters and noted the fact that several relatives asked questions concerning heredity, pointing out the physician's responsibility to be careful "not to scare the questioner half way to a psychosis . . . or to ignore the predisposition of these people to crack under life's stresses."

As compared with the psychoneuroses, the more dramatic, more circumscribed, more tangible psychoses adapted themselves easily to recording and statistical tabulations. Moreover, the coexistence of several cases of psychosis within the family group was relatively uncommon and therefore drew the scrutiny of investigators. In a more recent era, the psychoneuroses have come into focus as major problems, and the intrafamily conflicts so long hidden from view have been carefully examined.

A considerable gap has existed between these two large areas, that of the psychoses and that of the psychoneuroses—separated from one another by history, nomenclature, difference in methods of psychiatric training and discrepant levels of dynamic understanding. The bridges across this gap have increased at every point, until psychiatrists have arrived at broad, encompassing concepts of human behavior which make use of the older nomenclature for practical purposes only, while maintaining awareness of its inadequacies. Practical necessity still tends, in many instances, to segregate therapists into one group or the other. Most research projects are pragmatically limited by the same boundaries of surface symptomatology. Nevertheless, principles central to all the "functional" mental and emotional illnesses are being elucidated.

The problems of heredity, for example, have been explored carefully with reference to schizophrenia and the affective psychoses. Studies of mental illness appearing in several generations of one family have contributed to knowledge in this regard. Myerson studied a large series of cases illustrating the "horizontal" transmission of mental disease, reporting 2 instances involving 4 siblings and 1 involving 5 siblings. A closely related problem, which has been fairly widely examined, is that of the psychoses of association, or *folie à deux*. A recent exhaustive study of the literature by Gralnick (1942) yielded 103 cases of "communicated" psychoses, most of them involving 2 persons, but in 7 instances implicating 4 or more patients. In the numerous papers on *folie à deux* and multiple psychoses which have been reported, little reference has been made to the emotional impact of knowledge of the presence of the psychoses in the family on the normal members. Fear of inheritance of mental illness is, of course, widely discussed and easily understandable. In group therapy sessions conducted with psychoneurotic soldiers, for example, this problem was frequently brought up and insecurities and apprehensions of every degree on this score were laid open. Every psychiatrist has had to instruct and reassure relatives on this question innumerable times. The anxiety arising from the mental illness, especially a psychosis, of only one close relative may be considerable. When derangement seems to strike one's siblings one after another, misgivings about one's own future are appreciable.

The case described is certainly not an unusual one so far as it concerns the reaction of the patient to a threat, possibly greater than he could control. His insecurity is patent, and stands as one blade in a forest of insecurities of present day society. The special note comes from the presence of an unusual degree of severe mental illness in his kinship, constituting the menace to him. The steps from his feeling of vulnerability to the anxiety depression can be traced more precisely, in terms of his basic dependent personality, his undirected strivings for achievement, the significance of his successful marriage and, finally, the mounting precariousness of his position away from his family. Once the situation was changed, the relatively simple reaction subsided.

This case has been reported because it offers another small opportunity to break away from the shackles of a nomenclature which separates all mental illnesses into two large groups and tends to keep them divided. Had this patient been more deeply depressed, his illness might have been labeled a psychosis, and thus, through the vagaries of nomenclature, a "record" for mental illness in one sibship might have been built up. Sufficient data concerning the siblings are, unfortunately, not available in this case to analyze differentially the factors of association, heredity and intrafamily conflict.

SUMMARY AND CONCLUSION

The case of a soldier reacting psychoneurotically to the appearance of psychoses in 4 brothers and sisters is described. The reaction is readily understood, but is of additional interest in that it serves to draw attention to the chasm which divides the psychoses from the psychoneuroses. This gap has historical origins, is perpetuated by nomenclature and is, indeed, a practical necessity. Research and observation, however, may take cognizance of additional relationships between the two large groups of mental illness and may point to a future when more dynamic concepts will underlie nomenclature.

275 Central Park West.

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FIBRILLARY (PILOCYTIC) ASTROCYTOMA IN THE FLOOR OF THE FOURTH VENTRICLE

DWIGHT PARKINSON, M.D.
ROCHESTER, MINN.

ALTHOUGH Bailey¹ stated that astrocytomas may occur anywhere within the brain, the paucity of reported cases in the literature leaves the general impression that they do not arise from the floor of the fourth ventricle. None is so indicated in the most comprehensive reviews in the English literature² of the past fifteen years. A case of fibrillary astrocytoma of the floor of the fourth ventricle is therefore presented.



Fig. 1.—The astrocytoma (*A*) as it rests on the floor of the medulla (*M*), completely free in the cavity of the fourth ventricle except for the narrow attachment to the floor. The pons (*P*) was inadvertently sectioned before the tumor was noted. *C* indicates the corpora quadrigemina.

From the Department of Pathology, Dartmouth Medical School, and the Mary Hitchcock Memorial Hospital, Hanover, N. H.

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(Footnotes continued on p. 609)

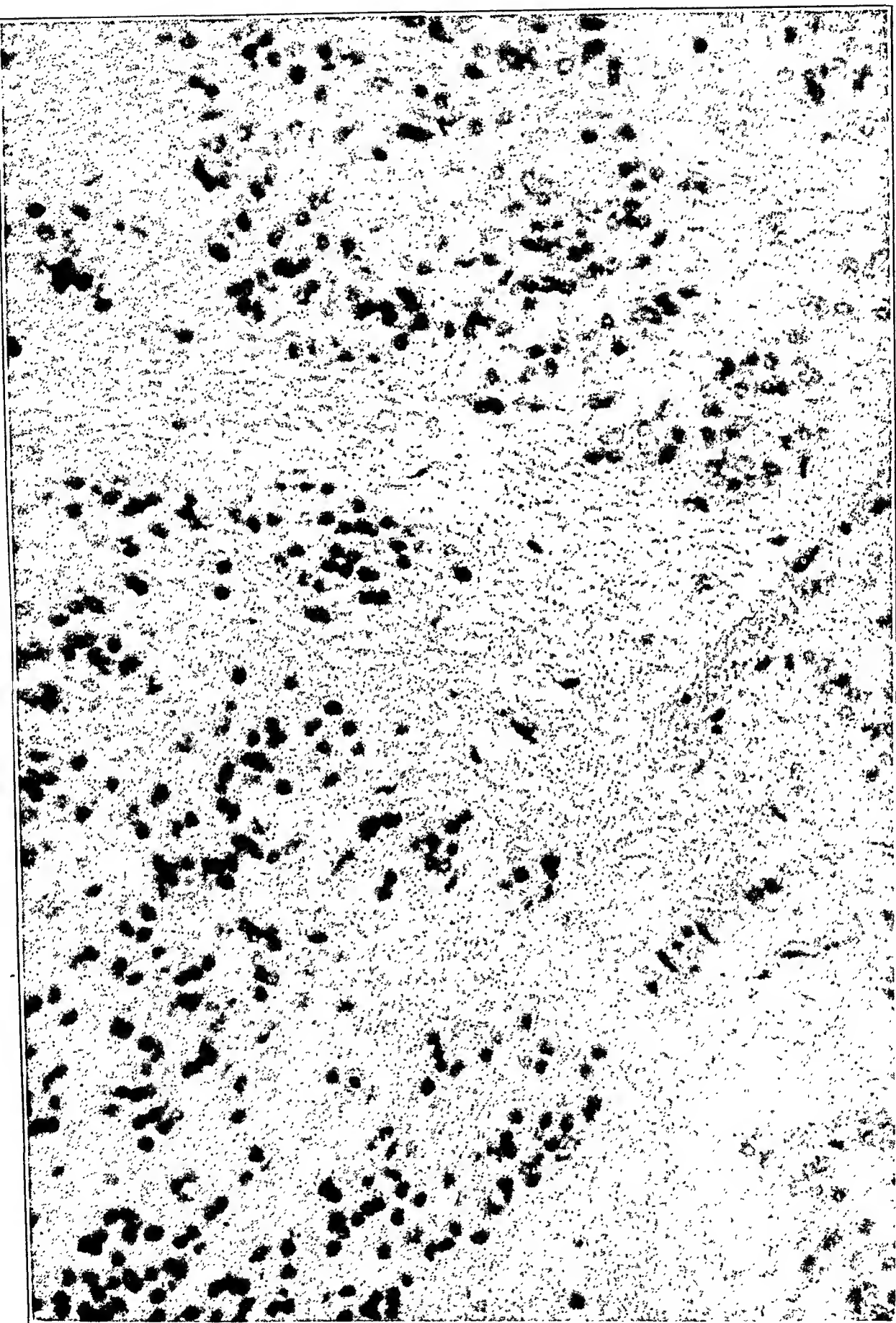


Fig. 2.—Microscopic section from the central portion. Phosphotungstic acid hematoxylin stain; $\times 40$.

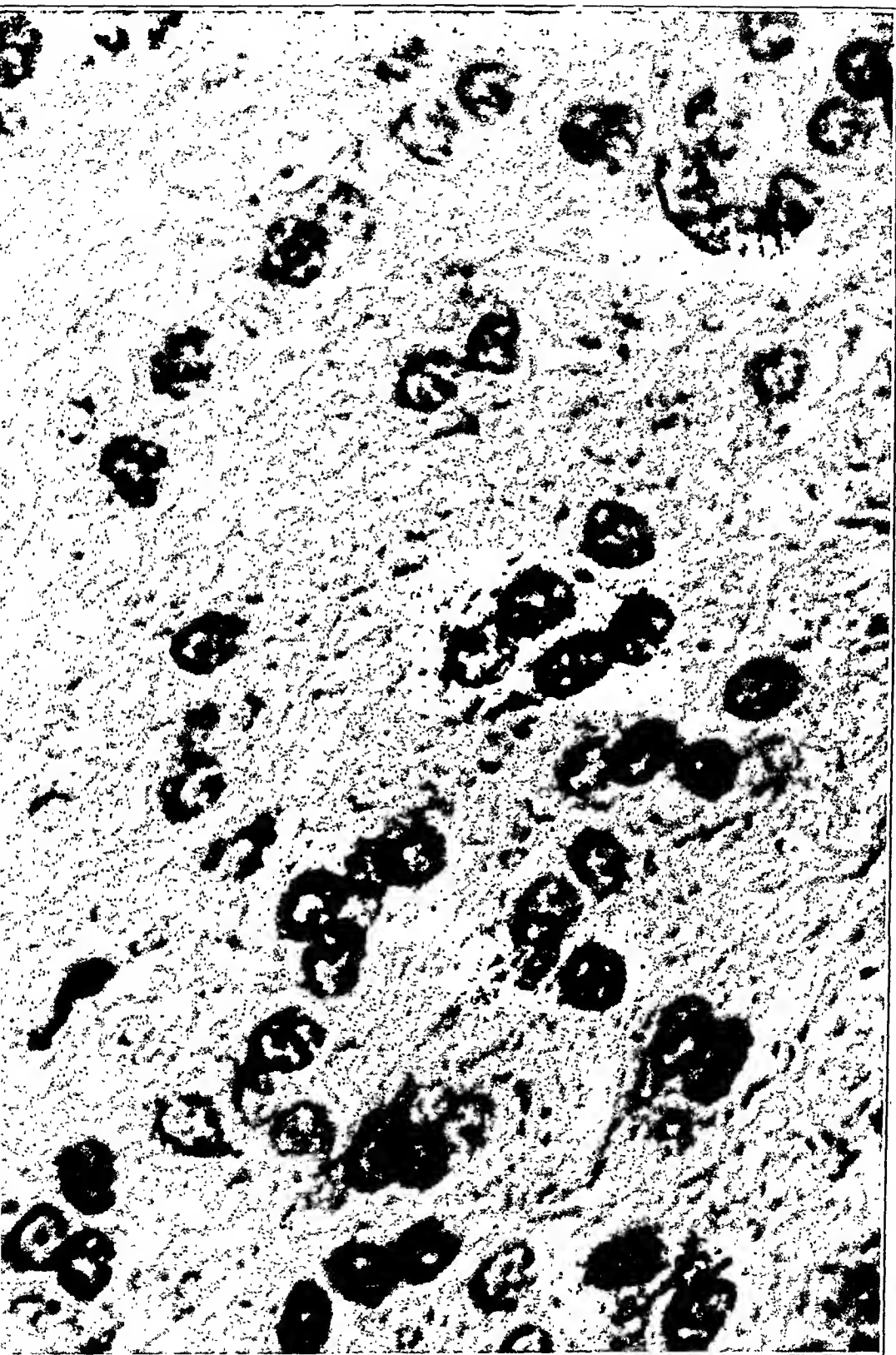


Fig. 3.—A portion of the field shown in figure 2; $\times 176$.

REPORT OF A CASE

H. B., a white woman aged 50, was admitted to the hospital with signs and symptoms of intestinal obstruction. Exploratory laparotomy revealed inoperable ovarian carcinomatosis with bilateral ovarian dermoid cysts. Death followed four days later as a result of pulmonary embolus.

At no time in her history or hospital course was there any evidence of intracranial tumor.

Routine examination of the brain revealed a firm, nodular, gray-white tumor, measuring 1.8 by 1.4 by 1.4 cm., in the fourth ventricle. It arose by a stalk 0.1 cm. in diameter from a point 0.5 cm. anterior to the obex and 0.2 cm. to the right of the midline (fig. 1). It had elevated the tela choroidea in the portion immediately over the tumor. There was no apparent interference with the outflow of cerebrospinal fluid at the foramen of Magendi, and there was no dilatation of the ventricular system. The sectioned surface was glistening gray-white, with no evidence of cyst formation.

Microscopically, with the hematoxylin and eosin stain, irregular clusters of vesicular nuclei were seen which appeared devoid of surrounding cytoplasm. Between these was a loose feltwork of eosinophilic strands, constituting the great bulk of the tumor and containing numerous small vessels. At the periphery the strands assumed a more orderly tangential arrangement.

With a phosphotungstic acid hematoxylin stain the nuclei and chromatin granules were dark blue with strands of the feltwork light blue (figs. 2 and 3). Some of these strands could be seen to terminate in dark blue expansions on the walls of vessels, which in contrast stained yellow-brown.

With the Gomeri silver method the nuclei, feltwork and capillary walls stained gray-brown and the larger vessel walls gray-pink.

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Special Article

REHABILITATION OF THE PARAPLEGIC PATIENT

COMMANDER EDWARD W. LOWMAN (MC), U.S.N.

OF ALL war casualties, the hope of none has received a greater boost than that of the paraplegic patient. What was once blank invalidism is now self sufficiency and independence. No longer need the paraplegic patient be an economic liability, a charge on society, sapped of self respect and initiative, confronted only by an empty horizon. His is a new perspective, a broader horizon, crystallized in the rehabilitation accomplishments of the recent war.

The attainments and advancements of the war were doubtless primarily the consequence of the large number of cases of traumatic transverse myelitis, which posed so urgent a problem that it became necessary to establish centers (nineteen in the Army, one in the Navy) for the specialized treatment of these injuries. The segregation thus in large numbers afforded the opportunity, the facilities and the personnel for mass observation, evaluation and standardization of treatment procedures. In one Navy hospital, 63 such patients comprised a group on which these observations are based.

The rehabilitation of the paraplegic patient is a joint undertaking, requiring the closest cooperation of the urologist, the neurologist and the physiatrist. The observations and advances of the first two have been adequately presented elsewhere.¹ It is the purpose here to discuss

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

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the role of the physiatrist and the proper application of his specialty, physical medicine (which comprises physical therapy, occupational therapy and physical reconditioning), to the problem.

The ultimate objective of physical medicine in the care of the paraplegic patient is self-sufficient reambulation. The steps in the attainment of this definitive result, briefly, are:

1. Maintenance of normal joint range for the prevention or correction of contracture deformities.
2. Development through resistive exercises of maximum power in remaining normally innervated muscle groups for use in reambulation.
3. Mobilization and utilization of all residual functional muscle tissue in partially denervated groups through serial muscle test evaluations, muscle reeducation and remedial exercises.
4. Prophylaxis against and treatment of decubitus ulcers.
5. Application of and instruction in use of reambulation devices for accomplishment of independent reambulation and normal personal care.
6. Encouragement of economic rehabilitation.
7. Maximum utilization of occupational therapy for functional, diversional and/or vocational objectives.

NORMAL JOINT RANGE

The maintenance of normal joint range is an imperative prerequisite to satisfactory reambulation.

The severe spasticity frequently encountered in the paraplegic patient and the prolonged disuse of joints secondary to the paralysis or to muscular weakness are both factors conducive to muscle shortening, which, in turn, is the precursor to contracture and contracture deformity. The cycle of spasm—muscle shortening—contracture deformity should be constantly borne in mind. The degree of reversibility of the cycle through physical medicine is in inverse ratio to the time lapse prior to institution of such measures. Treatment, therefore, must be instituted early.

From the start, each patient must be taught good bed posture in order to minimize postural deformities. Beds should be equipped with bedboards; and, when spasticity permits, the use of footboards for the prevention of mechanical foot drop should be insisted on.

In the presence of spasticity, heat (for its relaxing effect) is applied to the patient in bed for fifteen to thirty minutes once or twice daily, in accordance with the degree of pain. The involved joints, then, are carried to the extent of tolerance through a normal range of motion

with gradual, steady forcing to overcome the resistance offered by the spasticity. Massage for the spastic patient is generally poorly tolerated; this, however, is a general rule, and not infrequently light sedative massage will be well tolerated and will aid in providing greater relaxation of spasticity.

For the patient who can be transported by stretcher without aggravation of his spasticity (and most fall into this category), treatment can best be carried out in a Hubbard-Currance tank bath, the optimum water temperature being 98 to 102 F. (fig. 1). The effect of massage

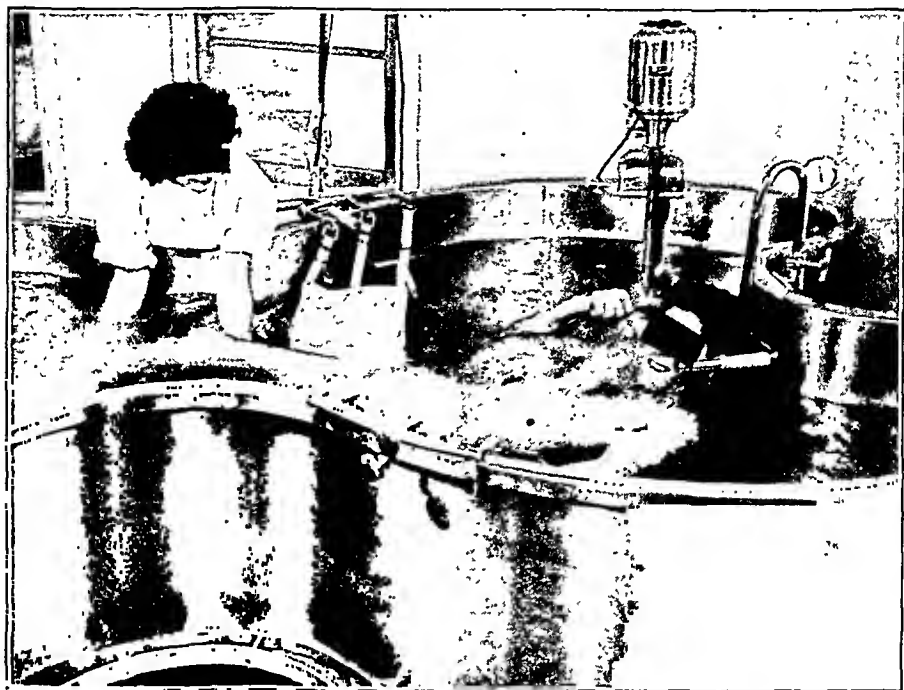


Fig. 1.—Hydrotherapy in a Hubbard tank should be prescribed early for the paraplegic patient.

provided by the underwater air ejectors may or may not, as in the case of manual massage, be well tolerated. Sessions in the tank are carried out daily for periods of thirty minutes each. Forcing of joints through normal ranges of motion and stretching of shortened muscles can be effected under water with much greater efficiency and less discomfort to the patient than at the bedside.

In the case of the flaccid patient, deep, sedative massage is employed routinely in conjunction with the procedures previously described for the maintenance of good circulation and nutrition of the skin and the prevention of orthostatic rubor, coldness and swelling.

As the patient acquires automaticity of bladder control and regularity of bowels, either voluntarily or by enemas, he is admitted to the

therapeutic pool. This pool is indoors; is heated at a constant temperature of 92 F.; is shallow, with a maximum depth of 66 inches (167 cm.), and is equipped with underwater plinths and walking bars. In the pool the patient receives further daily stretching (fig. 2), remedial exercises and muscle reeducation and graduates to standing and walking with the aid of the bars.

PHYSICAL RECONDITIONING

Physical reconditioning for the development of maximum power in unaffected muscle groups should be started immediately after the acute phase of the illness. Since efficient reambulation will be dependent



Fig. 2.—Restoration of shortened muscles to normal length and muscle reeducation can best be effected in a heated pool.

directly on the strength of remaining innervated muscle groups, so will it be expedited by maximum development of these groups. Bed exercises must be prescribed and carried out once, twice or many times daily, depending on the tolerance of the patient. At first they may consist of mild calisthenic procedures, such as breathing exercises, neck rolling, active arm and shoulder movements and abdominal tensing. They must be graduated progressively to resistive exercises. Each bed should be equipped with an overhead swinging ("monkey") bar. Resistive spring devices for arm, chest, shoulder and hand exercises are good agents to provide resistance for the bed patient.

Once the patient is out of bed, the regimen of exercises becomes more rigorous. In addition to his swimming exercise in the heated pool, he reports daily to the gymnasium and there begins mat exercises—exercises for the lower and the upper part of the back, push-ups, sit-ups, etc. Thus, building arm, shoulder and torso strength, he begins to utilize this strength in graduated doses, in lifting himself, ape fashion, with his arms from place to place around the mat, from mat to stool and then to higher stools, from stool to wheel chair and back, from wheel chair to toilet, from wheel chair to bath tub, from wheel chair to bed, etc. Progressively, he acquires increasing strength and self reliance.

MUSCLE REEDUCATION AND REMEDIAL EXERCISE

It should be the constant goal to mobilize and utilize to the fullest all residual functioning muscle. It should be remembered that much of the initial disability associated with traumatic transverse myelitis may be, and often is, a physiologic lesion, the result of edema, hemorrhage and compression of the cord, which may resolve quickly or persist until decompression by the neurosurgeon. This apparent partial reversibility has led neurosurgeons more and more to abandon conservative tendencies and to make surgical exploration early. Repeated muscle tests and persistent muscle reeducation must be carried out by the physiatrist or the physical therapist in order to maintain a valid evaluation and to effect best results.

In the case of weak muscles with partial residual innervation graduated strengthening exercises must be initiated, so that maximum function through hypertrophy of remaining intact muscle units may be obtained. In cases of very weak muscles, these exercises may at the start be electrically induced with apparatus, preferably painless galvanic-condenser machines. Underwater exercises, active or passive, with elimination of gravity, constitute the next step, and so on, to a level of resistive gymnasium procedures, depending on the potential capacity of the remaining intact muscle units. The latter must be prescribed, supervised procedures carried out with the aid and direction of the physical therapist.

DECUBITUS ULCERS

Decubitus ulcers are a constant hazard in the paraplegic patient and often occur despite the best nursing precautions. Bony areas with thin protective paddings of tissue are most predisposed to the production of pressure disruption of blood flow and consequent ulceration; common sites of predilection are over the sacrum, the femoral trochanters, the iliac crests and the heels. The best treatment is a vigilant prophylaxis—frequent changing of position (at least every two hours), use of rubber protective rings, prevention of friction burns from sheets, maintenance

of dry bedclothes, daily baths and daily massage of predisposed pressure areas. A common precipitant to be avoided is the trauma from careless shifting of the patient between stretcher and bed, inducing friction bruises.

Ulcerations are not a contraindication to Hubbard baths, but, on the contrary, are stimulated to more rapid healing by the heat of the water and by the massage effect of the underwater air ejectors. Daily local applications of ultraviolet radiation after this hydrotherapy is of therapeutic benefit in stimulating epithelization. The ultraviolet radiation is sometimes best applied with an applicator in order to reach undermined and sloughing deep areas.

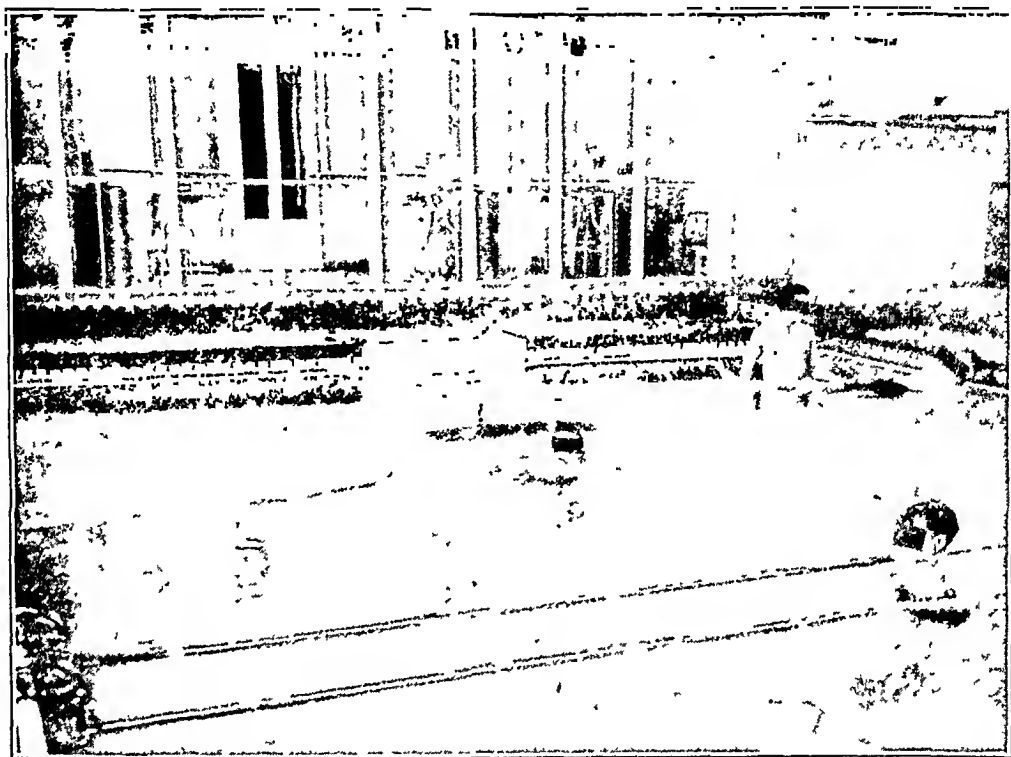


Fig. 3.—Vertical standing in a pool is the first stage in reambulation.

REAMBULATION

The vertical stance is best started with walking bars in the therapeutic pool (fig. 3). This renews the patient's acquaintance with upright posture and is a stimulus to his personal confidence, which will be needed for the mastery of reambulation on crutches and braces. For the patient with only partial paraplegia, stand-balance exercises, postural training, pelvic stabilization and weight shifting may be carried out for weeks or months in the pool before sufficient strength is attained to permit accomplishment of such feats against gravity.

Braces should be prescribed as soon as residual spasticity is sufficiently mild to permit their application. At best, braces are a crude mechanism and a poor substitute for normal means of body support

and locomotion. Each rehabilitee is in himself an individual problem and requires individualized evaluation before decision is reached on the type of bracing to be tried. Braces are locomotive aids, and, as such, augment means for ambulation; they should be built as a supplement to the patient's residual muscle power, and not as a substitute. Bracing should, therefore, be minimal within the bounds of necessity for the individual patient; this is particularly important in any case in which any degree of further return of functional strength is in the offing. Too

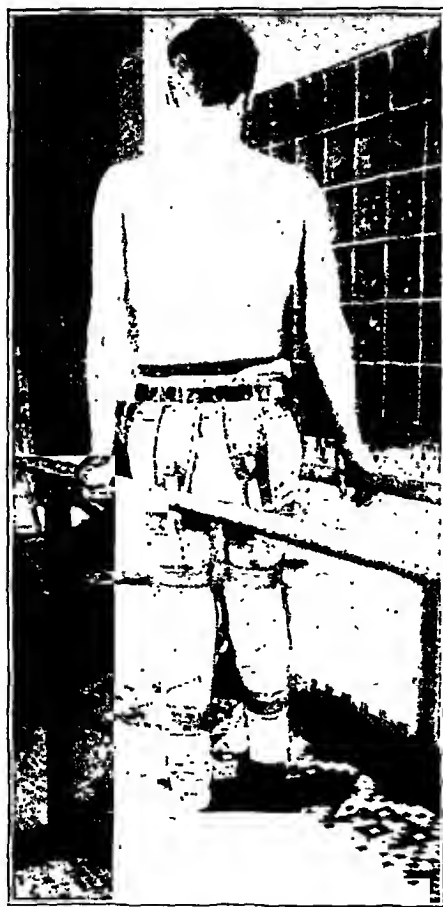


Fig. 4.—The stand-balance exercise and weight shifting are carried out in parallel bars with braces.

extensive bracing in such cases provides superfluous immobilization and thus removes the demand for work which is the cause of hypertrophy of the residual intact muscle units.

It is a great help to have the services of a well experienced brace maker, whose qualifications include not only technical skill and ingenuity but also a knowledge and appreciation of functional anatomy and body mechanics. The patient with a weak quadriceps muscle, for example, obviously presents a different problem from the patient with a paralyzed

quadriceps and should not be fitted with a long leg type of brace. Similarly, the patient with a weak anterior tibial muscle and normal peroneus muscles presents a different problem from the patient with peroneal palsy and requires different bracing. The cripple with loss of both the gluteal and the abdominal muscles requires considerably greater mechanical support than the patient with innervated abdominal muscles. Yet, too often bracing is standardized in broad types.

The decision for specific bracing depends on the individual picture presented by the patient's muscle test. Modifications in conformity with



Fig. 5.—Mastery of obstacles is imperative for maximum self sufficiency.

further need for support or with improvement in muscular power are to be expected and met. Not infrequently a patient may start with long leg braces and subsequently graduate to dropped-foot braces as the result of return of or increase in power in muscle groups.

Once braced, the patient must start the tedious and prolonged task of learning to utilize his residual muscle power in the manner most efficient for ambulation. First comes the stand-balance exercise, repeated day after day in parallel bars (fig. 4), at the foot of a bed or in a mechani-

cal walker. This mastered, he then must learn weight shifting from leg to leg to maintain balance. Finally comes the first step. In all of these procedures, the patient is putting to use the increased strength attained in the preceding weeks and months of bed and gymnasium reconditioning exercises. In learning walking, he relies at first on parallel bars, later on a mechanical walker and ultimately on crutches.

The type of crutch gait selected for the individual patient depends on the extent of his paralysis. With complete involvement of both lower extremities, the gluteal muscles and the abdominal muscles, a swing-through type of gait is the maximum accomplishment. As the degree of involvement decreases, the type of and need for crutch gaits, canes or braces vary accordingly.

With his aids to reambulation, the patient must be taught proper use for his maximum self sufficiency (fig. 5). He must master such ordinarily simple obstacles as stairs, inclines, curbs, toilets, automobiles, beds and chairs. He must be required before release to have attained at least an average dexterity in a standardized list of such feats of accomplishment. The subject of crutch walking and mastery of obstacles has been well covered in the writings of Deaver.²

ECONOMIC REHABILITATION

The sponsorship and encouragement of vocational training during the prolonged period of rehabilitation of the paraplegic patient are of the utmost importance. The pursuit of economic readjustment while he is still a patient provides not only sound preparation for return to society but is potent prophylaxis against inanition, introspection and the morbidity that often is bred of the idleness of prolonged convalescence. This is a medical problem which cannot be shifted elsewhere, but must be demanded and guided as such. The present hospital vocational training program in Veterans Administration hospitals for paraplegic patients is an admirable acceptance of this expanded concept of medical responsibility.

OCCUPATIONAL THERAPY

Occupational therapy fulfils a threefold function for the paraplegic patient. When functional results are desired, such as the correction of a deformity or the strengthening of a specific muscle group, the use of appropriate crafts or skills is to be carried out on prescription and under the direction of a trained occupational therapist. This, however, applies to only a limited group of patients. For all patients, diversional or

2. Deaver, G. G., and Brown, M. E.: Challenge of Crutches: Methods of Crutch Management, *Arch. Phys. Med.* **26**:397-403 (July) 1945; Challenge of Crutches: Crutch Walking, Muscular Demands and Preparation, *ibid.* **26**:515-525 (Aug.) 1945; Challenge of Crutches: Standard Crutch Gaits and How to Teach Them, *ibid.* **26**:573-582 (Sept.) 1945.

avocational arts and skills should be provided by occupational therapy. Such work may be carried out both in wards for the bed patient and in shops for the patient who is up and about. In this diversional work, the valuable aid of volunteer skilled civilian groups, such as the Red Cross Arts and Skills Corps, should be generously utilized. When, for certain patients, arts and skills may prove of vocational benefit, occupational therapy dovetails into and coordinates its work with the vocational training program.

MORALE

The maintenance of high morale in the paraplegic patient is dependent on (1) good medical and nursing care, (2) honesty with the patient and (3) the prevention of hospital fatigue through the maximum utilization of the patient's idle time in pursuits of a diversional, avocational or vocational nature. While verbally easy to analyze, this maintenance of morale is in many respects the most difficult actually to achieve, and, at the same time, the most important objective, for on its attainment largely rests the success of the entire program of both physical and mental rehabilitation.

SUMMARY

The successful rehabilitation of the paraplegic patient in wartime military hospitals has opened a new vista of hope for the "hopeless" cripple.

The rehabilitation of the paraplegic patient is the joint responsibility of the urologist, the neurologist and the physiatrist.

The objectives of physical medicine in the program are sevenfold: (a) maintenance of normal joint range for the prevention or correction of contracture deformities; (b) development of maximum muscle power in the remaining innervated muscle groups for use in ultimate reambulation; (c) use of muscle testing, muscle reeducation and remedial exercises for salvaging the maximum function from the damaged muscle units; (d) prophylaxis against and treatment of decubitus ulcers; (e) application of and instruction in use of reambulation devices; (f) encouragement of economic rehabilitation, and (g) maximum utilization of occupational therapy for functional, diversional and/or vocational objectives.

2030 Fairburn Street, Los Angeles (25). *

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

TERMINAL DEGENERATION WITHIN THE CENTRAL NERVOUS SYSTEM AS STUDIED BY A NEW SILVER METHOD. P. GLEES, J. Neuropath. & Exper. Neurol. **5:54** (Jan.) 1946.

Glees describes a silver method which gives excellent results with both frozen and pyroxylin sections, staining the nerve fibers in their terminal arborizations, both in the normal state and in the process of degeneration. With the latter it is necessary, first, to determine the appropriate time at which the degenerative process becomes histologically visible. This varies with the age and species and with the different parts of the central nervous system.

The silver method reported differs from the Bielschowsky method in two main respects: A different concentration of silver nitrate is employed, and preliminary treatment of the sections with the ammonia-alcohol solution (6 drops of ammonia in 50 cc. of alcohol) is introduced. This procedure dissolves the greater part of the myelin and thus provides the basis for a much more evenly stained section. Other advantages of the method are the perfect staining of the myelinated and non-myelinated fibers and the light brown color of the nerve cells. The staining of the nerve cells allows the more intimate study of the relation between the surrounding nerve fibers and the nerve cell protoplasm.

The term "terminal degeneration" is used to cover the degeneration of the terminals of the *bouton* type and the free nerve ending. The *bouton* type of degeneration within the spinal cord is on the whole very conspicuous, owing to the abundance of terminal rings in the normal state. This view has been arrived at not only by means of the technic reported here, but by other variations of the silver impregnation methods. Even with careful examination of the normal cerebral cortex, it is difficult to demonstrate ringlike endings. The synapse within the cortex is mainly represented by free terminals of the pericellular plexus.

GUTTMAN, Philadelphia.

DEVELOPMENT OF THE HUMAN LATERAL GENICULATE BODY. E. R. A. COOPER, Brain **68:222**, 1945.

Cooper, in a study of human embryos, observed that the lateral geniculate body derives its pars dorsalis from the lateral thalamic nucleus and that the pars ventralis is subthalamic in origin. The pars dorsalis is recognizable at the 22 mm. stage, at the time when the optic tract reaches this region of the thalamus. The pars dorsalis is the first nuclear mass to be differentiated in the thalamic portion of the diencephalon. The pars ventralis appears at the 35 mm. stage. Lamination of the lateral geniculate body does not appear until the sixth month of fetal life, and from the onset of lamination there are six U-shaped and V-shaped laminas, with their closed convex aspects placed laterally and ventrally. The optic tracts enter the ventrolateral convexities, and the optic radiations emit from the dorso-medial concavities. The four outermost and larger laminas are comprised of small neurons, while the two smaller and innermost laminas are made up of large neurons. Cooper disproves the previously held opinion of eversion of the laminas

in the human or the monkey lateral geniculate bodies, for the curvature in lemurs and in higher primates is always in the same direction and the convexity always receives the optic tract.

FORSTER, Philadelphia.

Physiology and Biochemistry

BLOOD OXYGEN SATURATIONS AND DURATION OF CONSCIOUSNESS IN ANOXIA AT HIGH ALTITUDES. CARL E. HOFFMAN, ROBERT T. CLARK JR. and E. B. BROWN JR., *Am. J. Physiol.* **145**:685 (March) 1946.

Hoffman, Clark and Brown observed subjects at simulated altitudes of 28,000 to 38,000 feet (8,500 to 11,000 meters) and studied (1) the periods of useful consciousness, (2) times to the appearance of tremor and imminent unconsciousness and (3) oxygen saturations of the blood at termination of useful consciousness, at appearance of tremor and at imminent unconsciousness. The times of imminent unconsciousness varied from one hundred and forty-one seconds, at 28,000 feet, to forty-seven seconds, at 38,000 feet. The time of useful consciousness was approximately three-fourths the time that consciousness was retained. Oxygen saturations of the blood averaged 64 per cent at the appearance of the first error and 56 per cent at the time of imminent unconsciousness.

FORSTER, Philadelphia.

INACTIVATION OF POLIOMYELITIS VIRUS BY "FREE" CHLORINE. G. M. RIDENOUR and R. S. INGOLS, *Am. J. Pub. Health* **36**:639 (June) 1946.

Newer knowledge on chlorine testing has made it possible to measure more accurately the concentration of free or uncombined chlorine in the hypochlorous state in organically polluted solutions. This is done by the orthotolidine-arsenite test. The test gives a measurement of the "free chlorine"; the combined chlorine, such as the chloramines, or the total available chlorine. In contrast to previous studies, this investigation showed that chlorine is an effective inactivating agent for the Lansing strain of poliomyelitis virus if related to the actual "free," or uncombined, chlorine residual in solution. The amount of "free" chlorine needed for inactivation is well within the range of doses used in water treatment and swimming pool sanitation when the "break point" method of chlorination is employed.

J. A. M. A.

RADIOTHERAPY AND INTRACRANIAL PRESSURE. MARIA BORISOVNA TSUKER, *Am. Rev. Soviet Med.* **2**:316 (April) 1945.

Tsuker reports her observations on the effect of roentgen therapy on the cerebrospinal fluid. Data are presented on a group of 19 adult dogs who were subjected to small doses of roentgen radiation. The following factors were constant for all experiments: current, 160 kilovolts and 4 milliamperes; filter, 0.5 mm. of copper and 1.0 mm. of aluminum; field, 13 by 18 cm.; target skin distance, 30 cm. Each treatment dose was 160 r, repeated three or four times, with a total dose of 480 to 640 r, or from three-fourths to one erythema dose. The vertex was the only field treated, and treatments were given at intervals of several days.

Spinal fluid was obtained through suboccipital puncture, performed one or more times. The initial pressure was compared with the pressure after the treatment provided there were no great fluctuations due to extraneous factors, such as fear. Determinations of the pressure were made on 13 dogs after exposure and were repeated several times, at various intervals, on 8 of the dogs. Sixty-five experiments on 13 dogs, before and after roentgen therapy, were analyzed.

The suboccipital puncture was always made under morphine anesthesia. The pressure was measured with a water manometer, which consisted of a U-shaped graduated glass tube filled with a weak solution of potassium permanganate and connected by a rubber tube with one outlet of a three way stopcock. The needle was attached by tubing to another of the outlets, while the third remained free and served as the control. Readings of absolute pressure registered on the manometer may not correspond to those on more sensitive standard manometers. Only the comparative pressure, and not its height before and after the treatment, was considered. Furthermore, fluctuations obtained with a more sensitive apparatus would be much wider than those obtained in the experiments. Measurements obtained on restless animals were discarded. Insufficient observation and infrequent readings are probable reasons for the discrepancies noted in various reports. It is necessary to make repeated determinations at various intervals after exposure.

The data indicate that, under the conditions described, intracranial pressure is lowered after roentgen irradiation. The decrease in pressure appeared immediately in about one-half the animals and became more pronounced later. Observations were terminated after six weeks, so that no conclusion on the duration and constancy of the lowered pressure is available.

In another series of experiments, on 6 dogs, the effect of roentgen radiation on the absorption of cerebrospinal fluid was determined. In these experiments, atropine sulfate and pilocarpine hydrochloride were introduced into the cerebrospinal fluid by suboccipital puncture. The times required for pupillary dilation and salivation were measured.

Analysis of the data shows that immediately after roentgen irradiation there was a considerable increase in the speed of absorption, but that the rate was not constant. In a few days to two weeks the increased absorption was followed by delayed absorption. The rate of absorption was further observed four to six weeks later in 4 dogs, in 2 of which it was studied twice. In 3 of the 4 dogs the rate approximated that before treatment, and in 1 dog the rate was considerably decreased after six weeks.

The rate of absorption varied at different intervals after roentgen therapy. Immediately after treatment absorption was accelerated, and during the next three to fourteen days it was delayed. This delay was more pronounced than the preceding acceleration but was variable as compared with the initial speed of absorption prior to roentgen treatment. The rate of absorption approached the original value after four to six weeks, and at times dropped below it.

The rapid increase in the rate of absorption may be explained by the effect of roentgen rays on blood vessels, producing hyperemia. Since the changes are physiologic rather than structural, the result of the action of roentgen rays on absorption is not constant.

Histologic studies were made on 10 dogs (9 adults and 1 puppy) subjected to roentgen radiation. Controls were prepared from 2 adult dogs and 1 puppy. Fibrosis was observed in the vascular network of all 10 dogs, with patchy areas in the stroma and subepithelial areas. In the 2 adult controls, but not in the control puppy, areas of fibrosis also appeared. In the puppy treated with roentgen rays, fibrosis was prominent. It is well known that vascular fibrosis in man may result from infections and intoxication. The development of fibrosis of the cerebral vessels in treated dogs may be due to repeated injections of morphine before the experiment and to the toxic effects of ether-chloroform anesthesia.

In the vascular fields of all dogs treated with roentgen rays, but not in the controls, deeply stained, shrunken epithelial cells were observed. The histologic

data correspond with those obtained by Schafer, Sgalitzer, Spiegel and others, who also noted pyknotic epithelial cells in the cerebral vascular networks after roentgen therapy of the skull.

In addition, cells with finely granular, pale-staining cytoplasm and large vesicular nuclei were seen. Some cells were smaller and vacuolated, with irregular margins. The controls had many more epithelial cells in stages of active secretion than had dogs treated with roentgen radiation. The cerebral vascular networks of dogs treated repeatedly with roentgen rays contained shrunken epithelial cells and only a few epithelial cells in an active secretory phase.

The effect of roentgen rays on intracranial pressure may be interpreted as follows: The lowered pressure of cerebrospinal fluid seen a few days after treatment is the result of accelerated absorption, and the lowered pressure seen two to six weeks later is the result of diminished secretion of cerebrospinal fluid, due to impaired function of the epithelium.

Tsuker states that these data may explain many contradictory clinical observations. Roentgen therapy is effective only in cases of hydrocephalus in which elevated intracranial pressure is caused by increased production or delayed absorption of cerebrospinal fluid or, frequently, by a combination of the two factors. In cases of hydrocephalus produced by mechanical obstruction of the cerebrospinal circulation, roentgen therapy is valueless. Favorable results in cases of communicating hydrocephalus were obtained, especially the acute form. Roentgen irradiation failed to relieve obstructive hydrocephalus. Roentgen therapy is most effective in cases of acute increase of pressure. With chronic hydrocephalus it is less satisfactory unless treatment is repeated frequently. Roentgen therapy is of value also in cases of injuries to the skull with increased intracranial pressure.

GUTTMAN, Philadelphia.

DISTRIBUTION OF INTRAVENOUSLY INJECTED FRUCTOSE AND GLUCOSE BETWEEN BLOOD AND BRAIN. J. R. KLEIN, R. HURWITZ and N. S. OLSEN, *J. Biol. Chem.* **164**:509, 1946.

Fructose (levulose) injected intravenously, in contrast to dextrose (*d*-glucose), does not maintain the electrical activity of brain or relieve symptoms of hypoglycemia in eviscerated animals. However, the rate of respiration of brain slices in the presence of fructose does not differ significantly from the rate in the presence of dextrose and the oxidation of fructose by broken cell preparations of brain follows the same pattern as that for dextrose. A hypothesis which would explain these findings is that the rate of transfer of fructose from blood to brain *in vivo* is not sufficient to provide a concentration of sugar that would meet the metabolic requirements of the brain. In the present work, the distribution of fructose and glucose between the arterial blood plasma and the cerebral hemispheres of cats was determined at various times after intravenous injection of these sugars. They are such as to indicate that the rate of transfer of fructose from blood to brain is considerably less than that of glucose. The concentrations of fructose found in brain were less than the concentrations of glucose required to maintain normal central function of the nervous system.

PAGE, Cleveland.

OBSERVATIONS ON THE MECHANISM OF ELECTRICALLY INDUCED CONVULSIONS. F. REITMAN and B. W. RICHARDS, *J. Nerv. & Ment. Dis.* **102**:421 (Oct.) 1945.

In order to test the significance of cerebral vasoconstriction associated with induced convulsions, a group of 16 patients receiving electroshock therapy were given intravenous injections of a preparation of nicotinic acid ("pelonin") in doses

of 50 to 100 mg. just before the application of a strength of current previously sufficient to cause convulsions. In 61 per cent of the patients the development of convulsions was inhibited by the drug. When amyl nitrite was given by inhalation to the same patients, convulsions were prevented in 59 per cent.

The authors believe that these results indicate that cerebral vasoconstriction is one of the basic mechanisms involved in electrically induced convulsions.

CHODOFF, Washington, D. C.

DORSAL ROOT POTENTIALS OF THE SPINAL CORD. J. C. ECCLES and J. L. MALCOLM, *J. Neurophysiol.* 9:139 (May) 1946.

Eccles and Malcolm studied the dorsal root potentials set up in the frog's spinal cord by either dorsal or ventral root volleys. The authors confirmed previously reported experiments and obtained additional information. The dorsal root potential was found to be a cataelectrotonic potential propagated electrotonically from a central focus and analyzable into an active, initial phase and a later phase of passive decay. Dorsal root potentials set up by strong or repetitive stimuli of the dorsal roots were found to have in addition a prolonged phase due to internuncial after-discharge, this phase being increased by convulsant drugs, such as strychnine, curarine and veratrine, whereas it was diminished by a narcotic, such as pentobarbital. Pentobarbital sodium was found to prolong greatly the time constant of delay but to have no effect on the rising phase. The dorsal root potential recorded in a dorsal root was found to be abolished during the spike of a maximum volley fired in through that root, and to recover in part during the decline of the spike. The dorsal root reflex which is often associated with the dorsal root potential conforms in all respects to the hypothesis that the impulses are fired by the cathodal polarization of the central terminals of these fibers. Eccles and Malcolm describe the mechanism of a reversed electrical transmission across the synapse.

FORSTER, Philadelphia.

A MIDBRAIN MECHANISM FOR FACIO-VOCAL ACTIVITY. A. H. KELLY, L. E. BEATON and H. W. MAGOUN, *J. Neurophysiol.* 9:181 (May) 1946.

Kelly, Beaton and Magoun observed before operation the potentialities of cats for facio-vocal expression and then produced bilateral lesions in the diencephalon or midbrain. Lesions of the hypothalamus at the level of the mamillary bodies, interrupting all known descending hypothalamic connections; interruption of the afferent paths to the thalamus; rostral lesions of the midbrain, and tectumectomy each failed to alter the facio-vocal activity of the cats. Central lesions in the mid-brain destroying the periaqueductal gray matter and adjacent tegmentum beneath the superior colliculus abolished or greatly reduced the facio-vocal activity. Stimulation of this region elicits facio-vocal behaviour. Kelly, Beaton and Magoun conclude that there is a central midbrain mechanism for integrating facio-vocal behavior in emotional expression.

FORSTER, Philadelphia.

BRAIN STEM FACILITATION OF CORTICAL MOTOR RESPONSES. R. RHINES and H. W. MAGOUN, *J. Neurophysiol.* 9:219 (May) 1946.

Rhines and Magoun observed the effects of exploratory stimulation of the brain stem on motor activity induced reflexly and by stimulation of the motor cortex in cats and monkeys. The authors found that cortically induced movements were facilitated by stimulating a mechanism in the ventral portion of the diencephalon which appears to receive functional contributions from the globus pallidus

and the nuclei of the midline and other thalamic nuclei. An uninterrupted continuity of facilitatory sites may be followed from the ventral portion of the diencephalon through the central gray matter and the tegmentum of the midbrain, the pontile tegmentum and the reticular formation of the medulla. Sites in the ventral part of the diencephalon stimulation of which facilitates cortically induced movements also facilitate motor activity evoked from the bulbar pyramid, even after cortical extirpation. Therefore the facilitation due to diencephalic stimulation is mediated within the spinal cord. Impairment of this facilitatory system in the brain stem may be responsible for the hypokinesia which follows experimental destruction of the globus pallidus and the ventral portion of the diencephalon.

FORSTER, Philadelphia.

TRANSMISSION OF IMPULSES IN PERIPHERAL NERVES TREATED WITH DI-ISOPROPYL FLUORPHOSPHATE ("DFP"). FREDERICK CRESCITELLI, GEORGE B. KOELLE and ALFRED GILMAN, *J. Neurophysiol.* 9:241 (May) 1946.

Crescitelli, Koelle and Gilman employed diisopropyl fluorophosphate in studies on the role of acetylcholine in the transmission of nerve impulses. Diisopropyl fluorophosphate has an irreversible anticholinesterase action. The experiments included in vivo and in vitro exposure of sciatic nerves to the drug, with subsequent study of conduction in the nerves. The authors found that local application of physostigmine or diisopropyl fluorophosphate in Ringer's solution to segments of isolated nerves led to block of impulses, indicated by failure to record action potentials in the nerve beyond the region of application. The block of impulses was not irreversible, for washing the exposed segment in Ringer's solution or merely removing it from the solution of diisopropyl fluorophosphate abolished the effect.

In vivo administration of diisopropyl fluorophosphate to bull frogs produced a reduction in the cholinesterase content of the nerves to a mean value of 2.3 per cent of that in control nerves. This indicated to the authors that the experimental nerves had virtually no acetylcholine-splitting activity. However, such nerves conducted impulses as well as control nerves.

Crescitelli, Koelle and Gilman conclude that there is no relation between the magnitude of the spike potential and the cholinesterase activity of the nerve fibers and indicate that the block produced by diisopropyl fluorophosphate was not due to anticholinesterase activity.

FORSTER, Philadelphia.

TREATMENT OF EXPERIMENTAL LIVER CIRRHOSIS. JAMES V. LOWRY, *Quart. J. Stud. on Alcohol* 6:271 (Dec.) 1945.

Albino rats at weaning were placed on a deficient diet (no. 545). They received 20 per cent ethyl alcohol as their sole source of fluid. A cirrhosis-like reaction of the liver was observed histologically in biopsy material which was removed sixty-three to eighty-four days after the rats were subjected to this regimen.

One group of the surviving animals continued to receive the same diet with the addition of 40 mg. of choline chloride daily; the other group received a similar diet and an increase in the casein content. All were given water for seven days after the biopsy. Then, some of these rats were placed on the alcohol regimen, but a few continued to receive the water. This treatment was continued for some animals up to a year.

The livers of the rats treated with choline chloride showed decided improvement in the gross and microscopic appearance. There was a lesser, but definite, improvement in the livers of the animals who had received an increase in casein. Although

therapy had no recognizable effect on the fibrous tissue present, it apparently prevented further progression of the cirrhosis and produced a notable improvement in the histologic appearance of the parenchyma.

BECK, Buffalo.

ALCOHOL AS A PREVENTIVE OF EXPERIMENTAL NEUROSES. JULES H. MASSERMAN, Quart. J. Stud. on Alcohol 6:281 (Dec.) 1945.

Ten cats were trained in successive stages to perform activities whereby the behavior patterns of each animal could be observed and graded according to a standard scale. The animals had to be induced to partake of alcoholic solutions, as normal cats refuse to drink them. After the behavior pattern of each animal was adequately determined under the influence of various doses of alcohol, the animal was subjected to shock stimuli that induced severe conflicts in the feeding situation. Only 3 of the animals exhibited a relatively mild neurosis when they had received 2 to 2.5 cc. of alcohol per kilogram of body weight.

When the conflicts were again induced in these 3 animals without ingestion of alcohol, they became severely neurotic. Five of the others, who had not shown emotional instability, also manifested strong neurotic behavior.

Masserman concludes that alcohol affords partial protection against the neurotogenic effects of conflictual experiences. This might be the result of one of the following mechanisms: diminution in the acuity of sensory experiences; disorganization of perceptual-integrative response formations, or impairment of retention of such reaction patterns as are temporarily formed. An attempt to correlate these observations with parallel phenomena in human behavior was made. Human beings have learned to drink alcoholic beverages either to cloud, and thereby mitigate, anticipated stresses, or as a hypnotic to blunt and disorganize neurotic anxieties.

BECK, Buffalo.

TRANSIENT DISTURBANCES FOLLOWING GUNSHOT WOUNDS OF THE HEAD. W. RITCHIE RUSSELL, Brain 68:81, 1945.

Russell points out that head injury from a blunt object produces instantaneous and widespread arrest of cerebral activity with relatively little focal injury, whereas injuries from missiles of high velocity produce predominantly focal signs, frequently without loss of consciousness. Wounds which present surgically no more than penetration of the scalp may overlie an area of cerebral bruising, with concomitant clinical signs. With small, superficial injuries of the brain the immediate effect indicates that the cortex has been rendered inert. Thus, injuries to the midrolandic area produce paralysis and numbness of the opposite upper extremity—the phenomenon of corticospinal shock. In the transient symptomatology sensory and motor components cannot be separated. With injuries to the motor region the lower extremity recovers from the shock state faster than does the upper extremity. The nearer the injury to the rolandic area, the severer is the transient sensory-motor disturbance and the greater the likelihood of permanent sequelae. The distribution of sensory loss after wounding tends to include the entire extremity. This effect is compared to the intra-areal firing by strychninization described by Dusser de Barenne. Deep pressure pain recovers quickly after rolandic wounds; cutaneous sensibility recovers slowly and incompletely. The remaining hypalgesia may be patchy and so slight as to be considered due only to cortical lesions. The induction of hypalgesia by cortical lesions is contrary to Head's concept that cortical injuries cannot alter the threshold for primary types of cutaneous sensation. The cortex of area 3 is buried within the rolandic fissure, and study of

penetrating lesions in this area reveals that they are associated with hypalgesia. However, permanent loss of all forms of sensation results only from limited wounds of the rolandic area, while gross injuries to the same area permanently destroy discriminative sensory functions only. This paradoxical situation is as yet unexplained. Hyperpathia, similar to the so-called thalamic syndrome, may occur with lesions of the postcentral gyrus.

FORSTER, Philadelphia.

A STUDY OF PUPILLARY INEQUALITIES IN MAN. ERIC A. TURNER, *Brain* 68:98, 1945.

Turner describes the use of cocaine and epinephrine drops in elucidating the underlying cause of pupillary inequality in clinical cases. The test was employed in 50 control cases and in 66 cases of pupillary inequality. The results suggest that the commonest cause of pupillary inequality in cases of head injury is partial paresis of the third nerve, in which pupillary changes may occur without external ophthalmoplegia. In cases of intracranial aneurysm Horner's syndrome of long standing may dilate but little and become irregular in outline.

FORSTER, Philadelphia.

INTRATHECAL PENICILLIN THERAPY: IMMEDIATE REACTIONS IN THE SPINAL FLUID. J. M. TAQUES BITTENCOURT, *Arq. de neuro-psiquiat.* 4:65 (March) 1946.

Taques Bittencourt reports on changes in the spinal fluid in 16 patients given intrathecal injections of penicillin. Fifteen patients had parenchymatous neurosyphilis, and 1, osteitis syphilitica with a normal spinal fluid. Prior to intrathecal therapy, the neurosyphilitic patients showed pleocytosis, with a count as high as 150 cells per cubic millimeter and a median count of 8 cells. In most cases the cells were lymphocytes. In 2 cases the cells increased to 600 per cubic millimeter, after treatment, and in 2 cases there were over 1,000 per cubic millimeter. The percentage of polymorphonuclear leukocytes increased as the cells became more numerous. Toward the end of the intrathecal therapy the spinal fluid became yellow, due partly to the penicillin and partly to the red cells in the fluid. In the case of osteitis syphilitica the cells increased to 152 per cubic millimeter, with 100 per cent lymphocytes. In all cases there was an increase in protein proportionate to the pleocytosis. The usual increase in protein was 5 to 10 mg. per hundred cubic centimeters. A greater increase was noted in 3 cases: In 1 case, with 100 cells per cubic millimeter in the spinal fluid after treatment, there was an increase in protein of 30 mg. per hundred cubic centimeters; in the second case, with 250 cells (72 per cent polymorphonuclear leukocytes), there was an increase of 60 mg., and in the third case, an increase of 190 mg., with no evidence of manometric block. There was no increase in protein in the case of syphilitic osteitis. The colloidal gold curve showed little modification. In a few cases the curve tended to become of mixed type. The Wassermann and Steinfeld reactions became more positive, for the hematoencephalic barrier permitted the more ready passage of antigens from the blood.

N. SAVITSKY, New York.

RELEASE OF PHOSPHORUS FROM ELECTRICALLY EXCITED BRAIN. VICENTE H. CICARDO, *Pub. d. Centro de invest. fisiol.* 9:115 (June) 1945.

The brains of 50 dogs, anesthetized with sodium pentobarbital, were stimulated electrically by means of an induction current. Specimens of blood were examined for phosphorus before and after electrical stimulation. In order to exclude the role

of muscular contractions, blood from the superior longitudinal sinus was compared with blood from the femoral artery and vein. Electrical stimulation was continued from two to five minutes. The method of Fiske and Subbarow was used to determine the phosphorus in the blood. A definite increase, up to 31 per cent, in the amount of phosphorus in the blood was noted after cerebral excitation by the electric current. After a rest of fifteen minutes the values often returned to normal. Repetition of the excitation sometimes caused an even greater amount of phosphorus to be liberated into the blood. The amount of phosphorus in the blood taken from the superior longitudinal sinus was always higher than that from the femoral artery or vein. In order more completely to exclude the role of muscular contractions, similar studies were made after section of the spinal cord just below the bulb. The same increase in phosphorus in the venous sinus was found after this procedure. The liberation of phosphorus was also not impeded by curarization of the animals. In the curarized animals, however, a second series of excitations after a rest of fifteen minutes did not result in as great an increase in the amount of phosphorus in the blood; the results were inconstant, and not very definite. In general, the amount of phosphorus obtained in curarized animals, even after the first series of excitations, was less than in the other animals. The author believes that curare impedes the liberation of phosphorus into the blood as the result of some central action.

N. SAVITSKY, New York.

Neuropathology

CENTRAL NERVOUS SYSTEM IN PNEUMONIA (NONSUPPURATIVE PNEUMONIC ENCEPHALITIS): II. PATHOLOGIC STUDY. H. H. NORAN and A. B. BAKER, *Am. J. Path.* **22**:579 (May) 1946.

Noran and Baker collected brain from 10 cases of pneumonic encephalitis in which complete necropsies were performed. In all instances evidence of encephalitis was established by microscopic study. The cerebral alterations were uniform throughout the entire series, even though the cause of the pneumonitis was highly variable. Extensive thrombosis and prominent perivascular hemorrhages were the principal microscopic lesions in the nervous system. The prodigious number of thrombosed cerebral vessels suggests that some alteration in the clotting mechanism of the blood may cause these cerebral lesions. The constancy of the cerebral lesions, regardless of the type of pneumonia, indicates that the real cause of encephalitis may be the pulmonary tissue itself. Some factor from the parenchyma of the lung may possibly accelerate intravascular clotting.

J. A. M. A.

DEGENERATION OF THE BASAL GANGLIA IN MONKEYS FROM CHRONIC CARBON DISULFIDE POISONING. RICHARD RICHTER, *J. Neuropath. & Exper. Neurol.* **4**:324 (Oct.) 1945.

Four monkeys (*Macaca mulatta*) served as subjects in this investigation. The animals were exposed daily, five days a week, to carbon disulfide vapor for approximately six hours each day over a period of twenty to twenty-one months. On several occasions acute intoxication, of an accidental nature, occurred. After death, complete serial pyroxylin sections through the cerebral hemispheres and through the cerebellum and brain stem of each animal were prepared. These were stained routinely with cresyl violet and by the Smith and Quigley method for myelin. Sections including the lesions were also prepared with the hematoxylin-eosin-azure stain, the Van Gieson method, the Holzer stain, and the Perdrau and Davenport methods of silver impregnation. Representative levels from the spinal cord were examined. Sections of parts of the brachial plexus and the sciatic nerves

from the thigh were stained with hematoxylin and eosin, with stains for myelin sheaths and by the Bodian silver method for axis-cylinders.

In all the animals the essential and pathologic changes consisted in extensive bilateral and symmetric necrosis of the globus pallidus and the zona reticulata of the substantia nigra. The monkeys presented in common profound motor disturbances characterized by reduction and slowness of all types of movement without pareses, absence of coordination in locomotion and climbing, plastic cogwheel rigidity of the skeletal muscles, flexor postural attitudes of the trunk and extremities and severe action and tension tremor. Richter states that the data justify the conclusion that the motor syndrome observed in the animals is attributable to destruction of the globus pallidus and substantia nigra and that there are close similarities pathologically and physiologically to the parkinsonian syndrome of man.

GUTTMAN, Philadelphia.

KORSAKOFF'S PSYCHOSIS: REPORT OF A CASE. M. REMY, *Monatschr. f. Psychiat. u. Neurol.* **106**:128, 1942.

Remy reports a typical case of Korsakoff's psychosis of ten years' duration which had an alcoholic basis. The anatomic changes were limited entirely to the mamillary bodies. In Remy's opinion, this case supports the conclusion that the mental disturbances characteristic of Korsakoff's psychosis are due to the cutting off of nerve impulses which normally travel along the tractus mamillothalamicus to the thalamus and thence to the cerebral cortex.

ROTHSCHILD, Worcester, Mass.

Meninges and Blood Vessels

ELECTROENCEPHALOGRAM IN SUBARACHNOID HEMORRHAGE. LOUIS GREENSTEIN and HANS STRAUSS, *J. Mt. Sinai Hosp.* **13**:76 (July-Aug.) 1946.

Greenstein and Strauss studied 29 cases of subarachnoid hemorrhage according to a method previously described by Strauss (*J. Mt. Sinai Hosp.* **9**:1-19, 1942). A definite correlation was found to exist between clinical cortical foci and focal abnormalities in the electroencephalogram. An electroencephalographic focus was found in 7 cases, in only 1 of which focal signs were absent on clinical examination. The electroencephalographic focus in this exceptional case was no longer present when a second recording was made, two weeks later. In 18 of the 29 cases only a meningeal syndrome was presented. Of these 18 cases, the electroencephalographic record was normal in 6, and showed a low degree of diffuse abnormality in 9, a high degree of diffuse abnormality in 2 and a high degree of abnormality with a focus in 1. Of the 6 normal records, 1 was obtained on the third day and 1 on the sixth day, with blood in the spinal fluid. Neither the finding of blood in the spinal fluid nor the presence of meningeal signs bore any relation to the electroencephalographic picture. In all cases the degree of abnormality in the electroencephalogram showed progressive diminution on repeated examinations at intervals of increasing length. No increase in the degree of electroencephalographic abnormality was noted in subsequent records once the hemorrhage had ceased. The authors believe that cortical changes due to the presence of blood cannot be postulated as the main cause of electroencephalographic abnormalities in cases of subarachnoid hemorrhage. They postulate that the diffuse electroencephalographic abnormalities may be due to a dysfunction of the deep centers close to the third ventricle. The deep centers may be easily affected in cases of subarachnoid hemorrhage, since many such hemorrhages arise from vessels at the base of the brain. The authors also point out the importance in differential diagnosis of

repeated electroencephalographic records. The diminution of electrocortical activity is against the diagnosis of a bleeding tumor and in favor of a subarachnoid hemorrhage due to some other cause.

N. SAVITSKY, New York.

Diseases of the Brain

ANALYSIS OF BRAIN ABSCESSSES OBSERVED DURING THIRTY YEARS. E. SACHS, *Ann. Surg.* **123**:785 (May) 1946.

Sachs says that during the past thirty years 142 cases of cerebral abscess have been observed at his clinic. In 128 of these cases the abscess was encountered at operation. In 12 of the remaining 14 cases in which the abscess was not located the patients were treated before the discovery of ventriculography. That the mortality at his clinic was higher than at other clinics he ascribes partly to the fact that he operated on every patient with an abscess of the brain, regardless of the seriousness of the patient's condition. He believes that an unencapsulated abscess should not be drained. During the acute stage penicillin is invaluable in bringing about encapsulation. Aspiration, except in cases of cerebellar abscess, should be used only as a palliative procedure until more radical treatment can be instituted. Excision without drainage is the ideal procedure, but frequently marsupialization must be resorted to if, in the course of an excision, the abscess has been ruptured.

J. A. M. A.

INVOLVEMENT OF CENTRAL NERVOUS SYSTEM IN INFECTIOUS MONONUCLEOSIS: REPORT OF TWO CASES. J. DE R. SLADE, *New England J. Med.* **234**:753 (June 6) 1946.

Slade cites 2 cases which illustrate the encephaloneuronic and encephalomyelitic types of infectious mononucleosis. In both cases there was evidence of permanent damage to the nerve tissue. At the time of the patient's admission the clinical impression was that of infectious mononucleosis. When the paralytic symptoms appeared, poliomyelitis was considered; but the Paul Bunnell titer in cases of poliomyelitis is not higher than 1:28. Clinical observations support the concept of infectious mononucleosis as a generalized infection with localization in one or more of the tissues or organs of the body. In the cases described there was apparently diffuse and spotty involvement of the nervous system. The clinical picture is similar to that produced by viruses of other diseases and suggests that this, too, may be a virus infection. Infectious mononucleosis is a potentially serious disease.

J. A. M. A.

Peripheral and Cranial Nerves

NUTRITIONAL DISORDERS OF THE NERVOUS SYSTEM IN THE MIDDLE EAST. J. D. SPILLANE, *Proc. Roy. Soc. Med.* **39**:175 (Feb.) 1946.

Two types of nutritional polyneuritis were seen among Polish troops and refugees after two to four years in Russian internment camps, with resulting widespread malnutrition. In the largest group of patients the symptoms antedated examination by six to twelve months. Sharp pains in the soles and the muscles of the calf resulted in difficulty in walking similar to that of claudication. Coldness and paresthesias of the feet were distressing symptoms. Muscular tenderness and atrophy and weakness of the extensors of the toes and feet, with sensory loss and reflex disturbances, appeared subsequently. The symptoms of the second group were characterized by the rapid onset of paralysis, in direct relation to an acute infective, debilitating illness. In a few fatal cases the Wernicke syn-

drome was observed clinically and at autopsy, but occasionally hemorrhagic changes were seen in the brain stem at autopsy where none had been demonstrated clinically. Intramuscular injection of thiamine improved the appetite and the pains but did not influence the period of incapacity or hasten restoration of muscular power or reflex activity.

In another series, of over 200 repatriated internees and prisoners of war, 20 to 100 mg. of thiamine hydrochloride given daily for one or two weeks failed to produce demonstrable improvement over the status of patients who received no additional supplement of vitamins.

BERRY, Philadelphia.

NOCTURNAL CHEIROBRACHIALGIA PARAESTHETICA: SCALENUS SYNDROME; STUDY OF 70 PERSONAL OBSERVATIONS. R. FROMENT and WEGELIN, *Presse méd.* **54**: 282 (May 4) 1946.

Froment and Wegelin report 70 cases of nocturnal cheirobrachialgia paresthetica occurring in 62 female and 8 male patients between the ages of 7 and 74 years, among whom were 59 between the ages of 30 and 60 years. One third of the patients were definitely neuropathic. The syndrome occurred in the upper extremities of the patients during the night and consisted of paresthesia of the fingers and of the hand, associated with pains of the sympathetic type in two thirds of the patients. Seventeen patients presented mild edema of the upper extremities. The disorder was elicited by the immobilization of the extremities and disappeared after energetic mobilization of the extremity involved. Many patients showed a spontaneous tendency to improvement, but there were also patients whose condition was refractory. Satisfactory results were obtained in 18 cases from treatment with sedatives, barbituric acid derivatives, antispasmodics and, occasionally, sympatholytic or vasoconstriction substances. This method of treatment was ineffective in 14 cases. Infiltration of the stellate ganglion was practiced in 8 cases, with satisfactory results in 2. The concept of sympathetic hyperexcitability supported by subclavicular venous stasis rather than that of a pathologic condition of the scalenus muscles is suggested for this condition.

J. A. M. A.

THIAMINE AND POLYNEURITIS DIPHTHERICA. K. WASSMANN, *Acta med. Scandinav.* **124**:27, 1946.

Wassmann treated 10 patients with postdiphtheritic paresis of the palate at the department of epidemic diseases of the Frederiksberg Hospital in Copenhagen. Five of the patients received one intramuscular injection of 20 mg. of thiamine hydrochloride in 2 cc. of distilled water, and the remaining 5 patients received 2 cc. of isotonic solution of sodium chloride daily for twelve to twenty days. The average duration of the paresis was twenty-six days in the vitamin-treated group and thirty days in the control group. There was therefore no convincing difference between the two groups. Paresis of the extremities was produced by injection of a mixture of diphtheria toxin and diphtheria antitoxin in 40 guinea pigs. Twenty animals were given intramuscular injections of large doses of thiamine hydrochloride, while the remaining 20 animals received no treatment. There was no pronounced difference between the vitamin-treated group and the control group with respect to frequency, severity or duration of the paresis or the time of its occurrence. Thiamine hydrochloride has no prophylactic or therapeutic effect on postdiphtheritic paresis in guinea pigs.

J. A. M. A.

Vegetative and Endocrine Systems

EXPERIMENTAL PITUITARY DIABETES OF FIVE YEARS' DURATION WITH GLOMERULOSCLEROSIS. F. D. W. LUKENS and F. C. DOHAN, *Arch. Path.* **41**:19 (Jan.) 1946.

Diabetes produced in a dog by injections of a pituitary extract was observed for five years and found to be of constant severity after the first year. Autopsy

revealed lesions resembling those which have previously been noted in cases of diabetes, viz., fatty deposits in the liver and the kidneys. In addition; intercapillary glomerulosclerosis, which has not hitherto been reported in association with experimental diabetes, was noted.

WINKELMAN, Philadelphia.

MATING BEHAVIOR IN MALE RATS CASTRATED AT VARIOUS AGES AND INJECTED WITH ANDROGEN. FRANK A. BEACH and A. MARIE HOLZ, J. Exper. Zool. **101:91** (Feb.) 1946.

Castration of male rats at ages ranging from 1 to 350 days was followed by a period of several months, after which the responses of the castrated rats to receptive females were tested. The capacity for sexual arousal was distinctly limited in all the castrated animals. The mating activity which did occur showed no relation to the age at which castration was performed.

Although the administration of androgen resulted in the appearance of the copulatory reaction on the part of all castrated males, the response was less complete in the rats castrated on the day of birth. The differences in behavior are probably due directly to inhibition of development of the penis. Replacement therapy failed to compensate for the lack of testicular secretion during the critical period of penile growth (from birth to 21 days of age).

The overt behavior of males castrated at birth to androgen given during adult life indicates that the essential neuromuscular mechanisms are fully organized and normally sensitive to the testicular hormone. The high proportion of incomplete copulations and the failure of ejaculation are the result of absence of a well developed penis, and hence of an important source of sexual stimulation.

REID, Boston.

Cerebrospinal Fluid

UPPER LIMITS OF NORMAL PROTEIN CONTENT OF THE CEREBROSPINAL FLUID. V. KAFKA, Monatschr. f. Psychiat. u. Neurol. **110:325**, 1945.

Kafka examined 500 cisternal fluids and found that the upper limit of the total protein content is 1.1 graduation marks, as compared with 1.3 graduation marks for the lumbar fluid. These values are equivalent to approximately 26.4 mg. per hundred cubic centimeters for the cisternal fluid and 31.2 mg. per hundred cubic centimeters for the lumbar fluid if the graduation mark of the special tube is accepted as equivalent to 24 mg. per hundred cubic centimeters. Kafka designates his method of determination as "protein relation," it being his aim to relate the individual values and compare them for different diseases. This method of protein relation is suited to the determination of the upper limits of the total protein content. Various observations have indicated that for the determination of the protein relation it is essential not only to ascertain the centrifugation time and the number of revolutions but also to determine the protein content of a graduation mark. If this is done, great differences will not be detected between the results of the protein relation and the Kjeldahl determination. It is also pointed out that the various modifications of the Kjeldahl method involve certain sources of error. The author further mentions a serial method which is a simple control and directs attention to numerous minor manipulations that help to avoid errors.

J. A. M. A.

Special Senses

NATURE OF STARVATION AMBLYOPIA. A. R. HAZELTON, J. Roy. Army M. Corps **86:171** (April) 1946.

Hazelton presents the results of a survey of patients complaining of dimness of vision among prisoners of war held by the Japanese in Thailand. The total number of patients examined was 277. The cause seemed to be bound up with a

combination of vitamin deficiencies. The disease resolved itself into two parts: 1. Easy exhaustion of the ciliary muscle, which was cured by the administration of thiamine hydrochloride, at least 1,000 international units intramuscularly per day for fourteen days. There were also the symptoms of eyestrain, i. e., pain in the eyeballs, frontal headaches, excessive lacrimation, heaviness of the lids and tired feeling of the eye, which increased after close work on reading and were alleviated by administration of thiamine. 2. A condition of degeneration of the cones of the retina, which was probably brought about by insufficient photosensitive substance for these receptors. The degeneration of the cones was shown by (a) lowering of the visual acuity, (b) inability to differentiate objects close together and (c) interference with color vision. The insufficient amount of photosensitive substance is postulated from the fact that the color of print changed on reading from black to green to yellow. Two facts emerge from this study: 1. There is a relation between eyestrain and thiamine deficiency. 2. Persons with avitophthalmia are liable to sustain further damage to their cones in bright light and so should not work in the sunlight and should wear dark spectacles. As the retina is of central nervous system origin, any degeneration of the organ is probably permanent; so the prognosis for these cases is bad. The results of treating patients with nutritional amblyopia of short duration with 10 eggs per day for thirty days were gratifying; all persons undergoing this treatment showed improvement, and 1 patient was cured.

J. A. M. A.

Encephalography, Ventriculography, Roentgenography

VALUE OF ROUTINE ROENTGENOGRAPHIC STUDIES OF WAR INJURIES OF THE HEAD AND NECK. GILBERT N. HAFFLY, Arch. Otolaryng. **41**:216 (March) 1945.

Haffly stresses the value of routine roentgenographic studies of all war injuries of the head and neck. He reports the case of an infantry officer who was struck in the left orbital region by a fragment of artillery shell. The left globe was enucleated, and a large ragged laceration of the left lower eyelid and adjacent region of the cheek was repaired with linen sutures within three hours after injury at a nearby evacuation hospital. Despite available roentgenographic facilities, no studies were considered necessary. Several days later, after he had been evacuated to the rear, routine roentgenographic studies revealed the presence of a comminuted fracture of the maxilla involving the inferior rim of the orbit. In addition, there was a large metallic fragment lying just below the left orbit close to the nares on the left side and within the cavity of the left maxillary sinus. The foreign body was disengaged with considerable difficulty and was found to be a fragment of an artillery shell, measuring 4 by 1.75 cm. Convalescence was uneventful.

RYAN, Philadelphia.

CEPHALHEMATOMA DEFORMANS: LATE DEVELOPMENTS OF INFANTILE CEPHALHEMATOMA. A. SCHÜLLER and F. MORGAN, Surgery **19**:651 (May) 1946.

A unilateral bulging of the anterior part of the skull was presented by a man and 4 women aged 20, 27, 54, 71 and 72, respectively. It was unusual for the patients to complain of symptoms referable to the cranial abnormality. Roentgenographic examination revealed an extensive hyperostosis as the basis of the deformity. Diploic hyperostosis prevailed in the calvaria and eburnated hyperostosis in the basal area. Osteoporosis and sclerotic islands; large, sequestrum-like fragments of bone, and sharply outlined cavities inside the diploe were characteristic features of the structure. Pneumatization was wanting or atypical in the hyperostotic area. The name cephalhematoma deformans seems adequate for this peculiar type of hyperostosis.

J. A. M. A.

Congenital Anomalies

ANALYSIS OF THE KLIPPEL-FEIL SYNDROME. C. A. ERSKINE, Arch. Path. **41**:269 (March) 1946.

In 1912 Klippel and Feil described the pathologic anatomy in a case of absence of the neck in a 46 year old man. The anatomic basis of the syndrome, since known by their names, consists essentially in congenital fusion and numerical reduction of the cervical vertebrae. Since the original description of this rare condition, most of the communications have been reports of clinical cases of a less extreme type. The three characteristic clinical features of the syndrome are shortness of the neck, limitation of movement of the head and lowering of the hair line.

From the case of the Klippel-Feil syndrome presented here, and from the cases reported in the literature, Erskine concludes that the essential features of the cervical deformity are synostosis of two or more cervical vertebrae and flattening and widening of the vertebral bodies. A numerical reduction of the vertebrae is an incidental, rather than an essential, part of the disorder, as is spina bifida. The latter depends largely on the degree of abnormality of the vertebral bodies. There is evidence that the anomaly has a genetic basis. A number of pathologic conditions which have been observed in association with the osseous deformity of the syndrome are explained in the light of recent observations in the field of experimental embryology.

WINKELMAN, Philadelphia.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Robert A. Groff, M.D., *Presiding*

Regular Meeting, May 24, 1946

Pneumococcic Meningitis Developing in a Patient Treated with Penicillin.
DR. CHARLES S. KAMBE (by invitation) and DR. ROBERT C. POPE (by invitation).

A case of pneumococcic meningitis with recovery was presented, thought to be of interest because the patient was receiving penicillin in therapeutic doses when the meningitis developed.

L. P., a man aged 49, who had been struck by an automobile, was admitted to the Episcopal Hospital on Feb. 22, 1946, in an unconscious state, with a compound fracture of the right leg and numerous other extensive lacerations, contusions and abrasions.

On his regaining consciousness and after improvement in his general condition, the patient was taken to the operating room, where, with the use of pentothal anesthesia, his wounds were debrided and dressed.

He was given routine postoperative care and treatment for head trauma, with the addition of 200,000 units of penicillin daily, given in doses of 25,000 units by intramuscular injection every three hours, and 100,000 units daily for two days, administered by continuous drip through a sterile catheter into the compound fracture wound.

For three days his condition was good; but on the morning of the fourth day he had a temperature of 104 F., leukocytosis, nuchal rigidity, severe headache and other signs of meningeal irritation. A spinal puncture revealed increased pressure and cloudy fluid, loaded with pneumococci.

Treatment consisted of intravenous and, later, oral administration of sulfadiazine in amounts which kept the blood level close to 20 mg. per hundred cubic centimeters, adequate intake and output of fluids, intramuscular injection of 400,000 units of penicillin daily and repeated spinal punctures, with the administration of 30,000 units of penicillin intrathecally once or twice daily.

The patient's course was especially stormy during the first week. His temperature fluctuated between 102 and 104 F., rectally; the pulse and respiration were rapid and irregular, and during most of this time he was semistuporous. Since the white cell count became normal on the eighth day and cultures of the spinal fluid had been sterile since the second day, all forms of medication were discontinued, on the possibility that they might be responsible for some of the symptoms. Though his condition was much improved the next day, he relapsed in another twenty-four hours and became delirious; so the previous therapy was continued.

It was practically impossible to make the lumbar punctures on this patient without considerable sedation; for this purpose, tribromoethanol solution U. S. P. and pentothal were found most useful. On one occasion, however, the same amount of tribromoethanol solution as that which he had previously tolerated easily produced oversedation, and emergency resuscitative measures had to be employed.

The patient slowly improved and on the seventeenth day seemed so well that the medication was discontinued. Six days later, however, he had a second relapse,

and the previously outlined therapy was again instituted, but with use of sulfamerazine. His further convalescence was essentially uneventful, and he was discharged on April 15, after fifty-two days.

The exact portal of entry was not determined, since cultures of secretions from the wounds and throat were sterile after onset of the meningitis. Attempts to type the pneumococcus were also unsuccessful.

DISCUSSION

DR. A. S. TORNAY: My colleagues presented this case, not to offer another cure of pneumococcic meningitis, but as a case in which meningitis developed during penicillin therapy and an organism sensitive to penicillin was found in the spinal fluid after onset of the meningitis.

A dose of 200,000 units of penicillin daily is as good as, or better than, the average dose used in treatment of most infections with organisms sensitive to the drug. The reason that meningitis developed in this case is not yet clear. I believe I am correct in stating that as yet the mechanism of control of infection in the nervous system with penicillin is not known.

As a result of our experience with this patient, I feel that in cases of cranial trauma with fractures through the frontal sinus, and possibly other parts of the skull, one should use a sulfonamide drug instead of penicillin as a prophylactic measure against the development of bacterial meningitis. In this particular case it was impossible to determine the source of infection. We felt that it was due to direct extension on the basis of trauma, but there was no roentgenologic evidence of fracture of the skull. Several features of the case were of interest during its management.

First, at the beginning of the meningitis itself, considerable difficulty arose because the patient exhibited evidences of increased intracranial pressure about every twelfth hour. Fortunately, regular spinal punctures seemed to control this complication. Another interesting thing about the course of the meningitis was the distinct tendency to relapse. The patient had two relapses during his hospitalization. I believe that for a year other relapses may occur.

I wish to thank Dr. Kambe and Dr. Pope for their excellent care of this patient. I, for one, did not expect him to live.

DR. GEORGE D. GAMMON: Did I understand the authors to say that penicillin was not as good as the sulfonamide drugs in cases of fracture of the frontal sinus?

DR. A. S. TORNAY: As a prophylactic agent in cases of cranial trauma I prefer the sulfonamide drug to penicillin.

DR. GEORGE D. GAMMON: I understood they meant the sulfonamide drugs were superior in treatment.

DR. A. S. TORNAY: No, they did not say that.

DR. GEORGE D. GAMMON: In the discussions at the meeting of the American College of Physicians last week, we were told of cases in which there was early development of resistance to chemotherapeutic agents. I wonder whether there has been any second study of the particular organism in this case to see whether resistance to penicillin had developed.

DR. A. S. TORNAY: On the first spinal tap, and possibly the second, the organism was recovered, but not after that; so no test of sensitivity could be carried out.

DR. ROBERT A. GROFF: This is an interesting subject and raises the question which Dr. Gammon has already asked—whether or not the use of penicillin as a prophylactic drug is dangerous.

From my experience, I should say there is a possibility that by using penicillin prophylactically one is in some instances making the organisms penicillin resistant. For that reason, I wonder whether one is justified in using penicillin prophylactically.

Was I correct in understanding Dr. Kambe to say that the fracture went through the frontal sinus?

DR. CHARLES S. KAMBE: No, there was no fracture of the skull. There was a compound fracture of the leg, but no other fracture.

Coccidioidomycosis: Report of a Fatal Case. DR. C. NELSON DAVIS.

A fatal case of cerebral coccidioidomycosis was reported. The diagnosis was established post mortem. During life the condition was considered to be either tuberculous or syphilitic meningitis, with the remote possibility of its being a torular infection.

Coccidioidomycosis is an endemic disease encountered in the San Joaquin Valley, in southcentral California, southern Arizona, New Mexico and western Texas. Most residents of these areas are infected with the coccidioides, but the infection is of a benign type. About 1 in 500 persons has the progressive form of the disease, which is disabling and usually fatal.

Man is considered to become infected by inhalation of the dust contaminated with the fungus or by entry of the organism through the skin after injury.

REPORT OF CASE

M. E., a Negro aged 27, single, was admitted to the veterans' service of the Philadelphia Naval Hospital on Oct. 19, 1944. He had been in reasonably good health until four months prior to his admission, when headache and a cough developed. These symptoms were progressive at the time of his admission. On admission, he complained further of night sweats, stiffness of the neck and occasional blurred vision. His symptoms persisted and gradually increased in intensity until he died, Jan. 25, 1945. In the final week of his illness he had periods of delirium, and he was in coma during the last forty-eight hours of life.

Neurologic Findings.—There were stiffness and tenderness of the neck. It was not possible to flex the chin on the chest. The pupils were sluggish; the deep reflexes were absent; the margins of the optic disks were blurred, and the left abducent nerve was paralyzed.

Ophthalmologic Study.—Both fundi showed papilledema. The surfaces of the disks were hyperemic, with several small retinal hemorrhages about each disk. The fields were contracted.

Electroencephalographic Readings.—There were some 4 and 6 per second and 8 per second waves throughout both hemispheres.

Laboratory Studies.—The urine was normal; the Kahn reactions of the blood and spinal fluid were negative. The sedimentation rate was 16 to 26 mm. in one hour. The white blood cell count was persistently high; the cell count of the spinal fluid was 280 to 468 per cubic millimeter; the protein of the spinal fluid was never below 100 mg. per hundred cubic centimeters. The spinal fluid pressure was persistently elevated, varying from 410 to 450 mm.

Pathologic Study.—The convolutions of the brain were somewhat flattened, and the sulci were smaller than normal. The pons and the lower part of the cerebellum were matted down with a pale fibrinous exudate. The ventricles were moderately enlarged. The upper cervical portion of the cord was softer than normal.

Histologic study showed an inflammatory reaction, with many large and small circular cells showing a thick refractile capsule. Many of these were within giant cells. These bodies were the spherules of *Coccidioides immitis*.

DISCUSSION

DR. H. C. SCHLUMBERGER (by invitation): What Dr. Davis said about the importance of this infection particularly from the point of view of the Army, is quite true. The Army Air Forces sent large numbers of men into the endemic areas. There, many of them were exposed to coccidioidomycosis, or San Joaquin Valley fever.

It is only fair to stress now that this generalized infection occurs only in about 0.05 per cent of cases of the disease. The generalized form is nearly always fatal. In about 40 per cent there is evidence of involvement of the central nervous system, usually meningitis.

At the Army Institute of Pathology my associates and I have autopsy records in well over 30 cases. In 23 cases the brain had been examined; in 15 there was definite evidence of cerebral involvement. In 13 cases there was meningitis, and in 2 of these there were also small foci in the cerebral cortex. In 2 cases in which there was no meningitis two small granulomas were present in the cerebral parenchyma.

It is interesting that in the cases of generalized infection there is frequently a negative reaction to the cutaneous test, whereas in cases with involvement of the lungs only the reaction is positive.

My colleagues and I had a case at the Valley Forge General Hospital of a soldier who had been stationed in one of the endemic areas. At autopsy, I could not find a focus in the lungs, although I looked for it, knowing that he had coccidioidomycosis.

DR. SHERMAN F. GILPIN: If I understood Dr. Davis correctly, I got the impression that it might be difficult clinically to tell this form of meningitis from tuberculous meningitis. I recall that he said that the chloride content was 580 mg. per hundred cubic centimeters. I wonder whether that was on more than one occasion, and whether the value went any lower than that. It is generally accepted that if the chlorides fall to 550 mg. per hundred cubic centimeters, one may make a diagnosis of tuberculous meningitis. Here, the figure was 580 mg., and the cell count, I believe, was consistent with tuberculosis. I should like to have Dr. Davis say a word about that aspect of the case.

DR. E. MARCOVITZ: At March Field, Calif., my colleagues and I saw about 200 cases of coccidioidomycosis. Of all that group, there was not a single one in which an infection of the central nervous system developed.

This case presented many signs of tuberculous meningitis. Also, there were signs suggesting greatly increased intracranial pressure, which might conceivably bring up the question of a cerebral tumor.

Long ago at the Neurological Institute I learned that when a case presented signs suggesting both tuberculous meningitis and cerebral tumor, the diagnosis was very likely to be meningitis due to *Torula* or some other yeast. I think this case corroborates that principle.

DR. ROBERT A. GROFF: Was this patient's death characteristic of increased intracranial pressure? It seems to me the entire problem was one of increased intracranial pressure.

DR. C. NELSON DAVIS: In answer to Dr. Gilpin's question, the value for the chlorides in this case was considered well within the normal range, although ordinarily 600 and 750 mg. is considered the range for chlorides. Dr. Rathmell

might explain that technical difficulty from the laboratory point of view. In conjunction with that finding, we had persistence of the cell count. The cell count did not gradually increase, as one might suspect with meningitis. The chronicity of the disease was also somewhat against a diagnosis of tuberculous meningitis.

I do not know whether or not this man was in an endemic area. His record could not be obtained at this time.

The patient had terminal pneumonia, and there was some infiltration around the vagus nerves. He had increased intracranial pressure and was severely emaciated.

Neurologic Complications of Diphtheritic Neuritis. DR. HERBERT S. GASKILL.

One hundred and forty cases of cutaneous diphtheria were studied in an Army general hospital with which I was associated. Of this group, multiple neuritis developed as a complication in 61, or 43 per cent. This figure for the incidence of neuritis as a complication is not accurate, since selection played a role in the patients admitted to the hospital.

The clinical picture of the multiple neuritis was characterized by its late onset and its slow, insidious development. The neuritis began either with symptoms referable to the cranial nerves, usually blurred vision, or with paresthesias, such as numbness and tingling of the hands and feet. The symptoms of involvement of the cranial nerve commonly lasted from ten to twenty days. They were followed by the sensory symptoms, at first merely paresthesias, but later objective signs of sensory loss involving all modalities—most commonly, diminution of pain and light touch sensibility. The sensory symptoms and signs usually persisted from six to ten weeks. Toward the end of this period evidence of motor involvement appeared in the severest cases. There was loss of the deep reflexes, together with weakness and easy fatigability of the extremities, and in a few cases atrophy of muscles. The motor phenomena generally recovered in about two months. The disease did not always pass through all these stages. The duration of the neuritis in the average case was one hundred days, but there was wide variation in this, depending on the severity of the neuritis.

Examination of the spinal fluid of all these patients disclosed an albuminocytologic dissociation. The increase in the spinal fluid protein was proportional to the severity of the neuritis in most cases.

The early use of diphtheria antitoxin appeared to protect against the development of multiple neuritis. All the patients recovered completely.

DISCUSSION

DR. GEORGE D. GAMMON: Dr. Gaskill has had an unprecedented experience during the war in seeing 140 cases of cutaneous diphtheria with neuritis. The only thing that approaches it is the experience of other observers in this war; Cameron and Muir, in the Near Eastern Theater, had 100 cases or so. The whole experience repeats that which was so beautifully written up by Walshe from his observations in Egypt in the first world war. The same problem is presented today as then: Are these lesions cutaneous diphtheria, or are they something else? What is the proof that these men had cutaneous diphtheria? The second question is: Where did they get the diphtheria? Was there an epidemic of nasal or nasopharyngeal diphtheria in the region at the time? In how many of these men were the ulcers the result of infection from the patient's own throat? What was the carrier rate for the population from which the material was obtained? In what percentage of the cases was Dr. Gaskill able to recover diphtheritic organisms from the ulcers?

I had experience with peripheral neuritis in Italy; Dr. Drayer can comment on that situation, as he was the neuropsychiatric consultant for the Fifth Army. His experience covered a long period and mine a short one. My associates and I saw cutaneous ulcers among the Germans, and we also saw diphtheritic neuritis. None of the ulcers were open at the time; so we were unable to obtain any cultures from the ulcers. The ulcers were punched out; they destroyed the whole skin. They were anesthetic and multiple. I think their incidence was about 30 per cent in the cases of neuritis which we encountered. Whether the lesion was of the same type as that which Dr. Gaskill saw is, of course, a question.

The Germans called them "dirt ulcers," among other things. Some of their men believed they were diphtheritic ulcers, and others thought they were not. Many studies were made in an attempt to prove whether they were diphtheritic or not; only a few gave satisfactory results.

We saw other patients who had had nasopharyngeal diphtheria, and we made the attempt to diagnose the neuritis as diphtheritic on the basis of bacteriologic studies and antitoxin titer of the serum. It is an interesting problem, for the diagnosis of diphtheria in retrospect is a difficult one. In a high percentage of cases the organism disappears from the throat in three weeks; the neuritis develops in six to ten weeks, so that by the time one sees the patient for the neuritis the chance of recovering the organism from the throat is slight.

Major E. B. Schoenbach made studies of the antitoxin level of the blood of these patients. The titer of their antitoxin was low, both for patients with diphtheria and for patients with diphtheritic neuritis. It was low as compared with that for the control population. There was no difference between the group with diphtheria in which neuritis developed and the group in which it did not.

Our efforts to identify the neuritis as diphtheritic from cultures of material from the nose and throat were failures because we saw the patients late and because the carrier rate for diphtheria in the population which we saw was 17 per cent. That is a very high rate. We could not spot a case as one of diphtheritic neuritis by culturing the secretion from the nose or throat or by determining the antitoxin level of the blood.

In making a diagnosis, then, it is necessary to depend on the clinical features of the disease. In diphtheria the paralysis of accommodation is specific. Palatal paralysis occurs with nasopharyngeal infections. I should like to ask Dr. Gaskill how often he saw it in the cases of cutaneous diphtheria. According to Walshe's theory, it should not occur. He looks on the palatal paralysis as due to local spread of toxin along the regional nerves, such as occurs in cases of local tetanus from spread of toxin in the regional nerves.

Another point which should be emphasized is the appearance of an increase in the protein of the spinal fluid in cases of diphtheritic neuritis, with the resultant confusion with the Guillain-Barré syndrome. Guillain was fully aware of this increase. In fact, he wrote an article on it before he published the description of his own syndrome. People like Gaskill and Livengood and Major Joe C. Johnson, in the Italian Theater, assembled data on cases of diphtheritic neuritis in this war which called attention to the older literature by numerous authors, and they expanded the observations. They have a much larger series of cases than the older literature contains.

I do not want to enter into a discussion here as to what constitutes the Guillain-Barré syndrome; that is a moot point. But it is important to realize that in cases of diphtheritic neuritis the protein of the spinal fluid may be elevated. I think that cases have occurred in civilian life in which the condition has been labeled the Guillain-Barré syndrome when it may have been diphtheritic neuritis.

DR. CALVIN S. DRAYER: Polyneuritis presented a problem in the Mediterranean Theater in that we saw a fair number of cases in which we were not at all sure of the etiologic agent. In many of them the picture resembled the Guillain-Barré syndrome, but the possibility of previous diphtheritic infection could not be ruled out. Thanks to Dr. Gammon and Major Schoenbach, we did find certain deficiencies in our laboratory setup. But, as Dr. Gammon has pointed out, we often saw the patient long after the diphtheritic infection had ceased to be in the stage at which the organism could be isolated by any known method.

DR. H. C. SCHLUMBERGER: What Dr. Gammon says about the Germans is of interest, for they were "tearing their hair out" because of the problems presented by diphtheria of all forms along the Eastern Front. Among the complications was one that has not been mentioned today, but which my associates and I saw in our own troops coming from the region where Dr. Gaskill was active. I refer to the cases of cardiac failure in which the patient dies suddenly and no one knows exactly why he died until culture of material taken at autopsy reveals the presence of *Corynebacterium diphtheriae*. Usually the Germans were able to grow organisms from such ulcers. Apparently, death occurred from heart failure a long time before the peripheral neuritis became manifest.

I had occasion to speak to Schaltenbrandt, a well known German neurologist. Schaltenbrandt told me they had had only 8 cases of the Guillain-Barré syndrome; obviously, then, they were not making the diagnosis of this syndrome in their diphtheritic cases, for they had literally hundreds of the latter along the Eastern Front.

DR. C. NELSON DAVIS: We had 11 cases of this disease, whatever it may be. Dr. Nicholas Klemmer and I reviewed the cases that came in from the South Pacific area, and we could not be certain that the men had diphtheria. There was no proof in cases from the forward areas that diphtheritic bacilli had been cultured successfully. The men did have a sore throat, but they all had been given diphtheria antitoxin combined with sulfanilamide, and it was impossible to tell whether they had diphtheria or not. They presented what may have been the Guillain-Barré syndrome. At least that is what we considered it, although at that time we were calling it toxic myelitis.

DR. CHARLES RUPP: I wonder whether Dr. Gaskill had any experiences with a case in which the antitoxin was given after the neuritic symptoms had appeared; and, if so, what effect, if any, it had on the neuritic symptoms.

DR. B. HERR: Did Dr. Gaskill try to correlate the virulence of organisms in guinea pig inoculations and the severity of the clinical infections?

DR. HERBERT S. GASKILL: I appreciate all the comments of the discussants, and I shall try to answer as briefly as I can.

I do not know where the soldiers contracted diphtheria. Diphtheria is endemic among the natives, for the local English doctors, who had been out there for many years, accepted it as a matter of course that diphtheria should occur. The disease was very different from the form seen in temperate climates. This point was brought out in a paper by Drs. Kern, Norris and others, who were on a hospital ship in the South Pacific. They soon discovered that many men with red, boggy throats, who clinically did not appear to have diphtheria, had the disease.

Let me cite briefly a case which supports this thesis. A medical officer in a forward evacuation hospital in our area was evacuated to our hospital because of a supposed myocardial infarction. He was known to have had a sore throat for two or three weeks before the so-called myocardial infarction developed. After he had been in the hospital several weeks, there developed neurologic signs and symptoms. He said that prior to the onset of the sensory symptoms in his hands he had noted

loss of accommodation. Objectively, neurologic examination revealed hypesthesia to pinprick in the distal segments of the extremities. We became suspicious then that he might have diphtheritic neuritis, for at that time neuritis developed in the first case of cutaneous ulcer.

Over one-half the patients with cutaneous diphtheria were admitted to the hospital at this time. They all came out of one campaign, the North Burma campaign. At that point we had, I think, only 3 cases from which virulent diphtheritic bacilli were cultured. Eventually, when we were sure that the diagnosis was correct, we radioed back to Washington and asked for a special medium to be flown out. We then found that virulent organisms were obtained in about 80 per cent of cases. Since the lesions did not differ clinically, it seemed reasonable to conclude that the organisms were the same in the two series.

Little is known about the carrier rate. It was exceedingly low so far as our hospital personnel were concerned. Few of them contracted diphtheria while taking care of the patients. There was no possibility of making studies on carrier rates in combat troops. The usual story was that the soldier acquired a blister or had a tick bite or insect bite which resulted in a small ulcer; this later became secondarily infected with diphtheritic organisms and finally developed into the chronic indolent ulcer of cutaneous diphtheria.

Palatal paralysis occurred in 7, or 11 per cent, of the cases.

Antitoxin was given after the neuritis began, not because we were trying to treat the neuritis but because Dr. Livengood became convinced that if the antitoxin was given by injecting it around the ulcer the healing of the ulcer was much more rapid.

There was no correlation between virulence of organisms and severity of neuritis. There was certainly no correlation as to the severity or number of ulcers and the severity of the neuritis.

DR. GEORGE D. GAMMON: In reply to Dr. Rupp's question: We saw about 3 out of 45 cases of diphtheritic neuritis in which the antitoxin was given late—by that I mean on the tenth, fifteenth or twentieth day after the beginning of a sore throat; in these cases a severe type of neuritis developed, which seemed to differ from the diphtheritic type. If the patient had neuritis already and if he was given the serum at the time he had the neuritis, the severity of the neuritis was increased promptly. In 2 other cases I recall that the antitoxin produced acute serum sickness, with hives and sudden abrupt neuritis with pain, which lasted about a week and cleared up; this was quite different from the diphtheritic picture. I want to point that out to see whether others have had the same experience.

NEW YORK NEUROLOGICAL SOCIETY

Irving H. Pardee, M.D., *President, Presiding*

Regular Meeting, Oct. 1, 1946

Presidential Address: Growth: Humoral and Genetic. DR. IRVING H. PARDEE.

Endocrine Manifestations and Their Relation to the Hypothalamus.
DR. CHARLES DAVISON.

It is well known that certain endocrine manifestations, such as water, carbohydrate and fat metabolism and gonadotropic functions, which were previously considered to be related primarily to the endocrine system, are at present thought

to be either of hypothalamic origin or under the neural control of the hypothalamus. The association of lesions of the hypothalamus with disturbances in the aforementioned functions has been proved experimentally and clinicopathologically. In some instances it was difficult to determine whether the resulting dysfunction was of purely hypothalamic or hypophyseal origin, or of both. For this reason, a number of observers believe these disturbances to be neurohormonal in origin.

It is definitely established that the hypothalamus is in intimate connection with the endocrine system. Of the various connections of the hypothalamus with the endocrine system the best known are (1) the supraopticohypophyseal tract, (2) the paraventriculohypophyseal tract and, possibly, (3) the tuberohypophyseal tract. Evidence for the existence of the last-mentioned tract is not yet entirely satisfactory.

Eleven cases in which necropsy was performed formed the basis of this presentation. There were 10 cases of tumor. Some of these invaded, while others only compressed, the hypothalamus. There were craniopharyngioma (2 cases), angioma (1 case), pituitary adenoma (1 case), suprasellar meningioma (2 cases), neuroepithelioma (1 case), ependymoma (1 case), hemorrhage of the hypothalamus (1 case), metastatic tumor (1 case) and epidemic encephalitis (1 case).

Lesions of the hypothalamus without involvement of the pituitary gland were observed in 6 of the 11 cases (cases 2, 3, 7, 8, 9 and 11), while implication of the hypothalamus and the hypophysis was apparent in 5 cases. The middle and caudal parts of the hypothalamus were more frequently involved than the rostral part.

Neurosurgery of the Parasellar Region. DR. JEFFERSON BROWDER.

Within and arising from structures adjacent to the sella turcica are encountered a great variety of tumors; some of these are neoplasms; others, retention cysts, and an occasional one is a large aneurysmal dilatation of one of the numerous large vessels that normally course by this region. To attempt to discuss all these lesions would take one entirely too far afield. Moreover, in well regulated neurologic clinics, recognition of most of these tumors has become commonplace, and appropriate surgical therapy has more or less been standardized. No longer does the removal of an adenoma of the pituitary gland or a meningioma in the suprasellar or the parasellar region arouse any more interest than is necessary for the assurance of a successful operation. I should like to venture only one comment concerning these two benign tumors. Far too frequently patients harboring such lesions are allowed to delay operation until the lesion has attained enormous size, thus jeopardizing not only life but, equally important, recovery of function of involved neighborhood structures following surgical removal of the tumor. Fortunately, from a diagnostic point of view, many of the meningiomas, as well as the pituitary adenomas, produce characteristic changes in the visual fields; consequently, such alterations in the function of the visual apparatus are sufficient evidence to warrant surgical exploration while the tumor is still relatively small. There are, however, certain types of neoplasms that arise from or secondarily implicate the hypothalamus concerning which surgical therapy is still somewhat controversial. Unfortunately, many of them are malignant, and therefore seldom curable. Occasionally an unexpected successful outcome may follow the removal of a malignant tumor, as the following brief case history attests.

In 1936 a 10 year old girl was admitted to the hospital with the complaint of headache and morning vomiting of three months' duration, unsteadiness of gait for two months, double vision and impairment of memory for one month and recent pronounced diminution of vision. There were lethargy, stiffness of the neck, a high degree of choking of the disk with secondary atrophy of the optic nerve, almost

if not quite complete blindness, weakness of the lateral rectus muscles and moderate ataxia of the extremities of the right side. Babinski's sign was present bilaterally. There was incontinence of urine. Ventriculographic study disclosed a considerable dilatation of the lateral ventricles and absence of air in the third ventricle. At operation the third ventricle was observed to be occupied by a soft, grayish pink tumor, about 3 cm. in diameter. The mass was removed except for what was thought to be a small piece of tumor tissue attached to the left internal cerebral vein. Histologically the tumor was an ependymoblastoma. Convalescence was relatively uneventful. A course of roentgen therapy was given (with a total dose of 2,800 r). Except for almost complete loss of vision, there was satisfactory recovery. The child entered a school for the blind and has made exceptional progress in her studies. In 1945, nine years after operation, she was readmitted to the hospital, and ventriculographic examination disclosed persistent moderate dilatation of both lateral ventricles and a slightly dilated, centrally placed third ventricle. It was concluded that evidence of regrowth of tumor could not be demonstrated.

This history indicates what may be accomplished in exceptional circumstances, especially when one is dealing with an ependymoma. Possibly surgeons have been too conservative in the treatment of slow-growing types of gliomatous tumors. More often, however, the neoplasm is obviously grossly invasive; consequently, an attempt at surgical excision will almost certainly lead to an early death.

In cases of invasive tumors obstructing the flow of cerebrospinal fluid, the establishment of artificial communications between both lateral ventricles and the third ventricle permits the fluid to by-pass the point of block, and useful life may be regained. In several instances, after this procedure, the clinical features representing hypothalamic dysfunction did not become evident for one to three years after operation, whereas in other cases the operation served only to precipitate death or to set up a chain of events that ultimately terminated in death.

The bright side of the picture for all concerned is the group of benign tumors; and once it is established by ventriculographic examination that the lesion is limited to the anterior aspect of the third ventricle, "hope runs high" that the tumor may be a paraphysial cyst, more commonly termed colloid cyst, of the third ventricle. The nature of this lesion need not detain us here, since it has been adequately discussed by Masson, Stookey, Dandy and McLean. It should be pointed out again, however, that the paraphysial cyst should be differentiated from the rarer cyst of the choroid plexus of the third ventricle. The epithelium of the cyst of the choroid plexus is nonciliated and lies on the external aspect of the cyst, whereas in the paraphysial cyst the epithelium is ciliated and lines the lumen of the cyst. In the average case the surgical removal of either type should not be technically difficult; however, care must be exercised to remove the paraphysial cyst totally, lest there be a recurrence.

While all these tumors, that is, chiasmal and hypophysial gliomas, cysts of the third ventricle, suprasellar and parasellar meningiomas, extrasellar extensions of hypophysial growths and others less commonly encountered, may and do functionally disturb the hypothalamus, it is the craniopharyngioma, or tumor of Rathke's pouch, that produces the most striking so-called vegetative disturbances, which are of considerable clinical significance but need no elaboration here. Surgeons have had the added opportunity to observe accentuation of abnormalities in vegetative features after attempts at total removal of either cystic or solid suprasellar craniopharyngiomas. Notably, there are pronounced tachycardia, arterial hypotension, mottling of the skin of the extremities, hyperthermia, diabetes insipidus

and, most striking of all, an alteration in consciousness, the state ranging from what appears as a peaceful sleep to obvious profound coma. In my experience, this somnolent state has persisted in some cases as long as eight days, occasionally terminating abruptly and the patient awakening in a manner simulating the springtime arousing of the hibernating animal.

Besides the problem of the clinicopathologic alterations produced by a cranio-pharyngioma, changes which have been thoroughly elaborated by many authors, there remains the unsolved question of satisfactory therapy for a lesion that in the majority of instances seems to be of a benign character. Surgeons, in particular, have been guilty of reporting a patient as cured from whom a cranio-pharyngioma has been removed, even though only two or three years has elapsed since operation. Simple aspiration of a cyst will at times result in cessation of symptoms for a comparable period; yet no one should hold that this procedure is more than a makeshift. From his vast experience, Cushing concluded that unless the lesion could be destroyed or inactivated *in situ* the mortality would doubtless remain high. Globus and others have noted that when the floor of the third ventricle and regional structures are grossly displaced they are commonly firmly adherent to the surface of the tumor. While some craniopharyngiomas are solid, the so-called adamantinoma, they are more often cystic. Of necessity, the only method of dealing with the solid tumors is excision, even though the procedure carries a high mortality. Some of the more commonly encountered cysts may be successfully treated by establishing a pathway for drainage between the cyst and the cerebral ventricular system, as advocated by Scarff. An alternate method of draining away the fluid elaborated by the inner lining of the cyst is excision of a part of the frontal lobe of the brain and drawing a part of the wall of the open cyst into the ventricular cavity. Any fluid elaborated by the epithelial surface of the cyst may be discharged into the cavity. Subsequently, if indicated, the cavity resulting from excision of the frontal lobe may be tapped and its fluid contents aspirated without fear of damaging cerebral structures.

DISCUSSION OF PAPERS BY DRS. PARDEE, DAVISON AND BROWDER

DR. WALTER TIMME: I remember that years ago, generations ago, practically the same discussion on the relation of the hypophysis and the hypothalamus was presented before this society as we have had this evening; I do not know whether there has been any progress in this field; it seems to me that the basis for discussion is still exactly the same. I wish particularly to speak of Dr. Pardee's address, which was of encyclopedic proportions. He discussed practically every type of growth function and dysfunction we have ever known, and the work of accumulating that material must have been tremendous. I congratulate him on the type and amount of work which he has accomplished. Some of the cases he presented are of the type we have discussed many times heretofore, and some are not. Some cases are interesting because of the difficulty of showing why, even with open epiphyses, growth cannot be produced to any extent. It has formerly been thought that with open epiphysial lines in the long bones utilization of the growth hormone of the anterior lobe of the pituitary was enough to stimulate growth materially. That is not so. Why is it not so? Many reasons can be proposed, but most of them are wrong; one of the most important is the antagonism of the pineal gland to the pituitary, and the pineal gland itself inhibits growth. One almost never takes into consideration the effect of the pineal body when presenting patients with lesions of the anterior lobe of the pituitary gland. That was brought out in a neurologic meeting two or three years ago by Loyal Davis,

of Chicago. He had done work on tumors of the pineal body and recognized the fact that some children began to grow after removal of a tumor of the pineal body, and he did not know why. The reason was the removal of inhibition of the pituitary gland. There is another reason. Secretions and extracts of the pineal body have an actual effect in reducing the speed of most growths. I have used such preparations successfully for that purpose, as in slowing the growth of the cancer cell; of course, it does not cure the cancer. Therefore, one must take into consideration such factors as the pineal gland when it is found impossible to produce growth by using preparations of the anterior lobe of the pituitary. It is sometimes impossible to determine the importance of the pineal gland; there is no way of measuring the effect of the gland except to assume it as a reason for inability to produce growth.

There is another point about the growth hormone of the anterior lobe. Riddle and Evans, of California, differed regarding the effects of prolactin (lactogenic hormone of the anterior lobe of the pituitary), described by Riddle who expressed the belief that this principle is the same as the growth hormone of the anterior lobe and produced growth by using the substance. Why? Prolactin has the effect of stimulating the mammary glands and producing by such stimulation a cessation of ovarian function, so that massive and intense hemorrhages, lasting for weeks and responding to no other treatment, will nearly cease after a few doses of prolactin. The effect is almost miraculous. The very fact that prolactin produces a negative disturbance in the gonads would indicate, as a corollary, that it would produce an increase of growth, for when the gonads are deficient growth proceeds more rapidly.

I am glad that Dr. Pardee mentioned the thymus gland as a factor in growth. The thymus gland is certainly the basis of accretion in the body. There is, for example, the accretion of bone. As Dr. Pardee mentioned, Rowntree showed in successive generations of his rats that feeding the animals thymus produced increased growth in their descendants. As a corollary of that observation, given a giant with a very small pituitary gland, the size of a pea perhaps, but with abnormally continuing growth, that growth may be stopped very rapidly by subjecting the thymus to roentgen radiation. In this case, it was the thymus that produced his gigantism, not the pituitary. Most of the long-legged giants have hypopituitarism, not hyperpituitarism. The growth is a thymic growth, as Dr. Pardee brought out.

The achondroplastic dwarfs are highly interesting. Most textbooks and most authorities declare that nothing can be done to overcome the achondroplasia. In nanism the legs are entirely too short and the upper part of the body is normal; and it is said that the deformity is congenital and nothing can be done about it. I had a young girl (brought to me by Dr. D. S. Bayard, of this city, a pediatrician), who appeared like a penguin at the age of $1\frac{1}{2}$ years. One could see only feet coming from below her little skirt; there were practically no legs to speak of. The prognosis was poor, but on presentation of the anterior lobe of the pituitary gland with some thyroid and calcium the girl grew both in intelligence and in height until she became a normal child, with a torso-leg ratio which was normal. The legs grew out of all proportion to the torso, and she became so normal, in fact, that she graduated from college, although that may not necessarily mean normality.

As for the Lorain dwarfs (persons with dwarfism and infantilism), they are almost perfect specimens of humanity, but small, and I have never been able to improve their height or stature. They are practically always normal in intelli-

gence, or even quick-witted, but nothing can be done regarding their height, as can be done with the achondroplastic dwarf.

I wish to congratulate Dr. Pardee on this useful presentation of the various anomalies of growth.

Dr. Davison's paper was highly complex. The relationship of the hypothalamus to the hypophysis and the other centers is so complicated that even with the most painstaking operative procedures one cannot be sure what one has done. I talked personally with Roussy; he expressed the idea that the hypophysis could be ablated without any effect on adiposity. I think Dr. Davison made a statement of that kind this evening. As a matter of fact, the ablation of the hypophysis was not complete, but left a certain number of pavement cells intact, and it is these pavement cells which have to do with adiposity; when these pavement cells are removed, adiposity results. These pavement cells are probably related to the cells of the tuber cinereum.

One of the important relationships of the hypothalamus to the hypophysis is that which exists between the mamillary body and the cortex. This relationship may produce the somnolence that frequently accompanies hypothalamic disturbances.

This summary shows my attitude toward what is being attempted in the field of hypophysial disturbances. The work that is done in the laboratory on hypophysial material must be checked and rechecked before any valid conclusions can be drawn.

DR. LEO M. DAVIDOFF: I shall confine my comments to the discussion of Dr. Browder's paper. Dr. Browder summarized the problem of the neurosurgeon, and he did it so well in the short time which he had that it would be ungrateful to add anything to what he had to say, for it would be taking advantage of the fact that he did not have time to say it. I should like only to state that recently I have changed my surgical approach to the colloid cyst, and also to the craniopharyngioma, in that I no longer make a transcortical incision into the ventricle but separate the two hemispheres of the brain and incise through the corpus callosum. The reason for this is that in cases in which a colloid cyst is approached through the cortex the patient sometimes has postoperative epilepsy. This is a distressing after-effect in a case in which the cyst has been removed successfully. With the trans-corpus-callosum approach one can avoid that difficulty. Another advantage is that, instead of approaching the foramen of Monro at an angle, one comes down on it directly, so that it is more easily brought into view.

With regard to the treatment of craniopharyngioma by removal of the frontal lobe and draining the open cyst into the cavity, I think Dr. Browder invented this operation, and it is an extremely useful one in certain circumstances, when the cyst is large and the walls of the cyst are adherent so that the tumor cannot be removed. It is sometimes life saving to be able to retap the cyst through the intact skull, and this method presents an opportunity for so doing, and doing it safely. Many methods have been invented for tapping the cyst through a previous trephine opening, but all of them are unsafe except in circumstances like this, in which the only thing between one and the cavity is a little scalp tissue.

In removing a craniopharyngioma completely there is not only the danger of injury to the hypothalamus but, as sometimes occurs, and occurred in a case of mine recently, the possibility of trauma to the optic nerves themselves. In this case, the patient, who was relieved entirely of his tumor, and cured from that point of view except for a slight degree of diabetes insipidus, was free from any serious endocrine disturbances but had reduction in vision. At first he was completely amaurotic, and now is able to see only shadows—a distressing result. In

approaching these histologically benign, but technically often difficult, lesions, the neurosurgeon must keep in mind the possibility of such an accident. It may be worth while to remember, too, that the late Dr. Frazier demonstrated in a series of cases of craniopharyngioma that the secretory activity of the cyst may be diminished, and sometimes completely destroyed, by the use of roentgen radiation; whether or not the actual destruction of the cyst takes place by this means is not certain, because some of these cysts seem to be discouraged in their fluid-forming tendencies simply by partial removal of the wall; nevertheless, from experience in a series of cases, it seems to me that roentgen therapy is helpful; therefore, when a cyst is not completely removed, it may be worth while to give the patient radiation therapy.

DR. JOHN E. SCARF: I have enjoyed these papers very much. I have two minor personal observations to contribute to the discussion. First, it is common knowledge among surgeons that complete removal of the pituitary gland and the contents of the pituitary fossa is practically never accomplished at operation, but in 1 case in my experience it did seem that at the end of the procedure, owing to the favorable configuration of bone, one could see actually the floor of the sella turcica, which was quite smooth, and that all glandular tissue had been removed. In this case the symptoms were unusual, and I should like to report them, without comment or deduction from them. The patient, whose principal difficulty, and only presenting complaint at the time of operation, had been referable to the optic nerve, exhibited the following symptoms after operation: First, he began to age; he actually seemed to shrivel up. Second, his body temperature fell, so that in the midst of summer he would be seen sitting in the clinic wearing an overcoat and a woolen muffler, actually shivering, and his body temperature would be 94 or 95 F. Third, he was subject to terrific cramps, which came on paroxysmally, involving various muscle groups. On one occasion I was reached on the telephone by a house officer at the patient's request. The patient at that time was in the anesthesia room of a hospital and was about to be operated on for a presumed "acute abdomen." I went at once to see him. He had intense spasms of the abdominal muscles, but I had seen similar spasms before, and I persuaded the surgeon to delay his operation. This the surgeon did, and the muscle cramps disappeared. This patient was thoroughly studied from many angles.

A second personal observation, in this case in connection with the hypothalamus, may be of interest. Several years ago Dr. Stookey and I devised an operation for the relief of obstructive hydrocephalus. This involved the passing of the instrument through the anterior wall of the third ventricle and on, posteriorly, through the floor of the third ventricle, in the region of the tuber cinereum and the mamillary body, leaving an opening 0.5 cm. in diameter through these structures, connecting the third ventricle with the interpeduncular cistern. The first time we did this operation we anticipated a serious disturbance in water metabolism, but none occurred. We have now performed this operation on approximately 20 patients without producing diabetes insipidus, even temporarily, in any of them.

DR. JOSEPH H. GLOBUS: Dr. Pardee has already given us a foretaste of what we are to expect for the rest of this term. Above all is his promise to complete sessions by 10:30 p. m., leaving me but a few minutes for the few remarks which I shall make. He has also demonstrated his ability to present highly instructive material and to provide us with an interesting program.

Dr. Davison has demonstrated in a convincing way something with which we are familiar, namely, that the hypothalamus has an important influence on endocrine:

functions. He presented a large number of cases, all with massive lesions in the hypothalamic region, either neoplastic or resulting from such growths. I should have liked to see more restricted lesions, so that correlation of the site of the lesion with the actual disturbance in function could be made with greater accuracy. The massive lesions demonstrated here have involved almost the entire hypothalamus, and the question arises whether they have not influenced other structures in the neighborhood of the hypothalamus. The demonstration has left the subject open once more, so that in another twenty years we shall probably have a program on the hypothalamus and then, let us hope, a similar study, but one which, by means of serial sections, may lead to careful correlation of the lesions thus observed and the manifestations presented by the patients under study.

Dr. Davison stated, with regard to polyuria and polydipsia, that he found only 1 case of craniopharyngioma in which diabetes insipidus occurred preoperatively. I have a collection of 15 craniopharyngiomas, and in almost two thirds of the cases diabetes insipidus was present preoperatively. In some it appeared after operation. In cases in which it was present before the operation it disappeared shortly afterward, to recur in some instances at a later date.

There is little I can say about Dr. Browder's paper except in praise, and that I have learned much from it about the way in which tumors in this dangerous situation can be approached.

DR. CHARLES DAVISON: I appreciate Dr. Globus' discussion. I am extremely sorry to disagree with him, but in most of the cases in my series the tumor was fairly well localized to the hypothalamus. I have emphasized that it is difficult to draw conclusions as to which part of the hypothalamus is involved; that of course is not my fault. In 5 of these cases the region was studied by serial sections.

With reference to the craniopharyngioma, I am sorry that I was misunderstood. I said that in a number of the cases of craniopharyngiomas polyuria and polydipsia occurred after operation. I cited the 1 case for this reason.

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following candidates were certified at a meeting of the Board in Chicago, Oct. 27 to 28, 1947:

Psychiatry.—By Examination: Albert Ackerman, Washington, D. C.; Edward T. Adelson, Newark, N. J.; Charles Carter Ault, Little Rock, Ark.; *Ruth I. Barnard, Topeka, Kan.; Edward R. Bennett, Staten Island, N. Y.; Murray Bergman, Newark, N. J.; Morris Binder, Northport, N. Y.; Aaron Harry Braverman, Bedford, Mass.; Elizabeth Lynn Bryan, Brooklyn; Allen W. Byrnes, Richland, Mich.; Ralph J. Carotenuto, Brooklyn; Abraham H. Center, Savannah, Ga.; Michael Chaplik, New York; Newman Cohen, Boston; Ernani D'Angelo, Jamaica, N. Y.; John A. Doering, Farnhurst, Del.; John Morris Dorsey, Detroit; Thomas Joseph Dredge, Greystone Park, N. J.; Raphael H. Durante, Philadelphia; Arnold H. Eichert, Sykesville, Md.; Benjamin B. Faguet, San Francisco; David M. Ferber, Brooklyn; Louis M. Foltz, Louisville, Ky.; Thomas Holland Fox, Fort Meade, S. D.; William Hanna Gallagher, Traverse City, Mich.; Harry M. Gardiner, Harding, Mass.; Simon L. Goldfarb, Hartford, Conn.; Walter Goldfarb, New York; Michael O. A. Grassi, Philadelphia; Sydney H. Green, Corte Madera, Calif.; Philip Samuel Greenbaum, Tucson, Ariz.; William Stone Hall, Columbia, S. C.; Isidore Holden, Los Angeles; Charles O. Holder, Kalamazoo, Mich.; Mansell B. Holmes, Tuscaloosa, Ala.; Frank J. Imburgia, Parma Heights, Ohio; Walter O. Jahrreiss, Baltimore; Simon Overton Johnson, Lakin, W. Va.; Ernest Frederick Jones, Marion, Ind.; Louis Kaplan, Philadelphia; Saul Howard Karlen, New York; Kenneth M. Kelley, San Francisco; Robert Coleman Longan Jr., Richmond, Va.; William H. Lyons, Detroit; Joseph Marcovitch, Marion, Ind.; Oswald John McKendree, Utica, N. Y.; Sol Brown McLendon, Columbia, S. C.; Edward Ray Miller, Beverly Hills, Calif.; John D'Arcy Morgan, American Lake, Wash.; James M. Murphy, Willard, N. Y.; Elsie S. Neustadt, Quincy, Mass.; John Joseph O'Connell, Ontario, Canada; Robert P. Odenwald, Suffern, N. Y.; William D. O'Gorman, Omaha; Albert Lamoin Olsen, Fort Custer, Mich.; Helen Joyce Perrin, Des Moines, Iowa; Max J. Primakow, Wood, Wis.; Charles Prudhomme, Washington, D. C.; Charles R. Rayburn, Norman, Okla.; Irving Salan, Orangeburg, N. Y.; Louis Schlan, Chicago; Henry Z. Shelton, Orangeburg, N. Y.; Roy C. Sloan, Lubbock, Texas; Willie Mary Stephens, Chicago; Nina Toll, Middletown, Conn.; Clarence A. Vallee, Batavia, N. Y.; Comdr. Robert Lowell Wagner (MC), U. S. N.; David Michael Wayne, Fort Meade, S. D.; Joseph E. Weber, Milwaukee; Paul Wenger, Bedford, Mass.; Mabel G. Wilkin, Bethesda, Md.; *Emil Guenther Winkler, Long Island, N. Y.; Joseph A. Winn, New York; Robert L. Worthington, Topeka, Kan.; Bernard Yood, Boston.

Psychiatry.—On Record: Anthony Trevisano, Castle Point, N. Y.

Neurology.—By Examination: Ernest A. Burrows, Providence, R. I.; *Carl M. Epstein, Topeka, Kan.; *Samuel Futterman, Los Angeles; John William Magladery, Baltimore; Lewis Alan Roberts, New York; John Hallman Taeffner, Philadelphia; Samuel Wood Weaver, Santa Ana, Calif.

Neurology and Psychiatry.—By Examination: Raymond L. Osborne, New York; John Leopold Simon, New York; Miguel Steinberg, New York.

* Denotes complementary certification.

Book Reviews

Mental Mischief and Emotional Conflicts (Psychiatry and Psychology in Plain English). By William S. Sadler, M.D. Price, \$6. Pp. 396. St. Louis: C. V. Mosby Company, 1947.

This book was written for the "average" person who wants to know more about emotional conflicts—most likely his own. It is an excellent idea, but the author runs into the same difficulty that all technical writers do in attempting to simplify complicated mechanisms. The result is either an oversimplification or an incomprehensible hodgepodge. This book suffers from being both. There are passages which are simplified enough to make them interesting, but which, unfortunately, strain the facts. There are also long and detailed classifications which the technical reader would have to classify as original but meaningless.

The book tends mostly toward description, and only chapter headings indicate the dynamic aspect. The author describes the illnesses very well, but when he begins to explain the basic origins of the disorders he becomes once more descriptive and not very helpful.

This book was read with the purpose of evaluating its usefulness to the average reader. If an average reader wants to go through 372 pages of purely descriptive material, he is not an average reader. With such a seductive title, the reader is entitled to a better and clearer study of mental illness.

Diseases of the Nervous System. By F. M. R. Walshe, M.D. Price, \$4.50. Pp. 351. Baltimore: Williams & Wilkins Company, 1947.

This short, simple text has gone through five editions in six years. This in itself is evidence of a need for such a book. The author has held it deliberately on a practical level, omitting all procedures and considerations not accessible to the practicing physician. As much as the wisdom of the clinical approach to a clinical field is to be admitted, the reviewer cannot help feeling that the author carries it to a point of condescension toward his readers. Might not the practicing physician like to be shown new lines of thought, even though he cannot test them with his own tools? The brief chapter on the psychoneuroses is inadequate.

The Engrammes of Psychiatry. By J. M. Nielsen, M.D., and George N. Thompson Jr., M.D. Price, \$6.75. Pp. XIX, plus 509, with 28 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1947.

This textbook presents a system of biologic psychiatry. The authors are seeking the engram patterns which underlie human behavior. In the anatomic and physiologic introduction (chapter I), they state that for the functional activities of conation, consciousness, instincts, will, cognition, personality and emotions, one must recognize (a) a brain stem component, (b) a diencephalic component and (c) one or more cortical components. Thus, conation, which is defined by the authors as the tendency to move and is considered by them to be the most fundamental of all cerebral functions, depends on a motor mechanism made up of three levels of cerebral structures: (a) the periaqueductal gray matter, (b) the ventrolateral nucleus of the thalamus and (c) the precentral and postcentral Rolandic area (chapter II). A lesion in the periaqueductal gray matter will render the patient devoid of desire to move.

For the complete functioning of consciousness, there exists, likewise, a neuronal system involving the brain stem, the diencephalon and the cerebral cortex (chapter III). A crude form of consciousness is mediated by the brain stem and the diencephalon. The engram system, which is essential to crude consciousness, is located

at the junction of the mesencephalon, the subthalamus and the hypothalamus. Lesions of the thalamus cause loss of attention, i. e., loss of the capacity to focus awareness.

Those instincts which are present at birth have their neuronal patterns in the diencephalon and the brain stem (chapter IV). These instincts are: crying; sucking; defensive reaction against falling; holding the breath and bearing down in evacuation of the bowels and bladder; turning the head and eyes in response to light and sound, and response to coddling. Instincts which require perception, recognition and organized concepts for their execution require also the cerebral cortex. Emotion is described as the result of the facilitation or the impediment of an instinctive drive and is expressed fundamentally by engrams in the hypothalamus (chapter V).

The authors define personality as the habitual reaction patterns of the person (chapter VII). The engrams of personality also have a brain stem, a diencephalic and a cortical component. The cortical site of lesions causing change in personality is primarily in the cingulate gyrus—frontal lobe engrams, and in the case of the frontal lobes chiefly in the orbital cortex. The functions of perception, recognition and recall are, with one exception, cortical functions in man (chapter VIII). The exception is man's capability of crude perception of touch and pain without the cortex.

Psychoneuroses are defined as mental mechanisms of defense and represent partial failures (and necessarily partial successes) in meeting frustrations (chapter XII). A psychoneurosis is an unconscious confession of defeat in one sphere of activity but with preservation of the personality as a whole. The authors believe that the psychoneurotic and the psychopathic personality are incompatible (chapter XIX). The pathognomonic sign of the psychopathic personality is the failure or inability to make practical use of the concept of time.

The basic pathologic feature of schizophrenia, the authors postulate, is an engrammatic disorganization of the diencephalon (chapter XI). This is indicated by the early symptoms of apathy, emotional paucity and loss of interest and attention. As the schizophrenic process continues the cortical functions become implicated. The symptoms found in manic-depressive psychosis are related to the level of activity of the diencephalon (chapter XVI). In the depressed phase of the illness there is a depressed (but not disorganized) function of the diencephalon. In the manic phase, on the contrary, the diencephalon is stimulated. The authors postulate that in the involutional psychosis there is a partial diencephalic disorganization along with endocrinal involution (chapter XVII). Paranoia is considered to be the psychotic rationalization of failure in the predisposed person (chapter XVIII).

This book reflects the extensive interest and experience of the authors in problems of the pathologic physiology of the brain in relation to disturbances in mental functioning and behavior. The authors are expounding, as they see it, the anatomic and physiologic substratum of psychiatry. They have presented the existing evidence, both experimental and clinicopathologic, from their work and that of others in support of their hypotheses. They are aware of the gaps in the present knowledge of the subject. Much of what they present is tentative and subject to later revision. The book is stimulating and is bound to give rise to controversy. It will be criticized by some for its lack of approach from the standpoint of Gestalt psychology.

The style of writing is refreshing and readable. Case histories are well chosen. The book contains much practical information for the practicing psychiatrist and the psychiatric student. The book is well indexed and well illustrated and contains a bibliography of the works cited.

CENTRAL NERVOUS SYSTEM IN PNEUMONIA (NONSUPPURATIVE PNEUMONIC ENCEPHALITIS)

III. An Experimental Study

H. H. NORAN, M.D.

A. B. BAKER, M.D.

AND

W. P. LARSON, M.D.

MINNEAPOLIS

THE CEREBRAL complications associated with pneumonia have received but scant attention in American literature, although numerous reports are available in many of the foreign journals (Bonaba, Marcos and de Agorio¹; Comby²; Bonaba, Boni and Barberouse³; de Filippi and Fernández⁴; Nové-Josserand and associates⁵; Gareiso and Sagreras⁶; Mollard and Dufourt⁷; Eschbach⁸; Stephan⁹; Comby¹⁰). Actually, such complications are not infrequent and may appear at the onset or at the height of the pneumonia or during convalescence, after the patient has become afebrile and appears well along the road to recovery. Cases often reveal a wide variability of symptoms,

From the Division of Neurology, the University of Minnesota Medical School. This study was aided by a grant from the John and Mary Markle Foundation.

1. Bonaba, J.; Marcos, J. R., and Mendivil de Agorio, S.: Nuevos casos de encefalitis neumónica, *Arch. de pediat. d. Uruguay* **12**:317, 1941.

2. Comby, J.: L'encéphalite aiguë chez les enfants, *Arch. de méd. d. enf.* **10**:577, 1907.

3. Bonaba, J.; Boni, E., and Barberouse, C. M.: Tres nuevos casos de encefalitis post-neumónica, *Arch. de pediat. d. Uruguay* **8**:245, 1937.

4. de Filippi, F., and Fernández, I.: Encefalitis paraneumónica, *Arch. argent. de pediat.* **11**:22, 1939.

5. Nové-Josserand, L.; Rougier, and Feuillede: Névraxite consécutive à une pneumonie chez une enfant de 4 ans; guérison, *Lyon méd.* **153**:272, 1934.

6. Gareiso, A., and Sagreras, P. O.: Encefalitis agudas en los procesos infecciosos, *Rev. argent. de neurol. y psiquiat.* **2**:233, 1936.

7. Mollard, J., and Dufourt, A.: Sur l'encéphalite aiguë au cours de la pneumonie, *Lyon méd.* **66**:821, 1911.

8. Eschbach, H.: Pneumopathies à manifestations cérébro-méningées, *Arch. méd.-chir. de Province* **27**:47, 1937.

9. Stephan, B. H.: Des paralysies pneumoniques, *Rev. de méd., Paris* **9**:60, 1889.

10. Comby, M.: Les encéphalites aiguës post-infectieuses de l'enfance, Thesis, Paris, Masson & Cie, 1935.

ranging from such generalized complaints as headache, vomiting, vertigo and lethargy to the more dramatic complications of coma, convulsions, delirium, monoplegia, hemiplegia, athetoses and psychic disturbances (Baker and Noran¹¹). The most common picture seen is that of acute meningoencephalitis. In many instances, after a short period of generalized symptoms, a severe delirium or convulsions of a focal or generalized nature may develop (Mollard and Dufourt,⁷ Reimann,¹² Stephan,⁹ Comby,² Eschbach,⁸ Garzón¹³). Since these cerebral complications generally appear at the height of the illness or at the time the acute infectious process is subsiding, they have been suspected of being merely the result of a toxic condition or of pyrexia.

Significant cerebral complications of pneumonia, however, may occur a few days to a few weeks after the patient's temperature has returned to normal, at a period when recovery would seem inevitable. There is generally a dramatic and abrupt onset of lethargy and stupor, often associated with focal motor symptoms. The severity of the pneumonic process plays no part in the incidence of these complications. Recovery is usually delayed and improvement is slow, often leaving permanent sequelae.

In an attempt to investigate the nature of the resulting cerebral changes, the nervous system in 10 fatal cases was studied in detail (Noran and Baker¹⁴). It was observed that the pathologic alterations were similar in each case regardless of the etiologic agent causing the pneumonia. The changes varied only in degree and severity. The cerebral lesions consisted primarily of thrombi or intravascular clots and petechial hemorrhages. In the milder cases many of the smaller vessels were partially or completely occluded by homogeneous material, within which special stains often revealed interlacing strands of fibrin. In the cases of severer involvement this vascular thrombosis or clotting was more extensive, implicating a relatively large percentage of the vessels. Blood vessels of all sizes were partially or completely occluded by these clots. Mild hemorrhagic lesions were not infrequent, and vascular congestion was prominent. Many of the smaller occluded

11. Baker, A. B., and Noran, H. H.: Changes in the Central Nervous System Associated with Encephalitis Complicating Pneumonia: I. A Clinical Study, *Arch. Int. Med.* **76**:146 (Sept.) 1945.

12. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, *J. A. M. A.* **111**:2377 (Dec. 24) 1938.

13. Garzón, W. P.: Meningoencefalitis postneumónica, *Med. de los niños* **35**:261, 1934.

14. Noran, H. H., and Baker, A. B.: The Central Nervous System in Pneumonia (Nonsuppurative Pneumonic Encephalitis): II. A Pathologic Study, *Am. J. Path.* **22**:579, 1946.

vessels were surrounded by a zone of erythrocytes or by areas of mild perivascular demyelination. In the 10 cases studied the etiologic agents causing the pneumonia were variable, including a nonhemolytic streptococcus, a staphylococcus and a type III pneumococcus, and in several cases the disease was the so-called virus pneumonia. Probably the most remarkable case was that of encephalitis following a typical lipid pneumonia, the presence of which was confirmed by fat stains. The fact that the cerebral lesions were similar regardless of the etiologic agent or process causing the pneumonia suggested that they were probably produced by some product of the injured lung tissue rather than by an infectious agent.

In an attempt to produce experimentally the lesions of pneumonia encephalitis, various animals were inoculated intravenously and intra-arterially with the filtrate of homogenized lung tissue. It soon became apparent that all animals were extremely sensitive to intravenous inoculation of small amounts of "homologous" lung extract, that is, an extract of lung tissue of the same species of animal. Heterologous extracts (extracts of lung tissue of a different animal species) had little or no effect on the animal, even when given in much larger amounts. For example, from 0.5 to 1 cc. of a 1:25 dilution of rabbit lung extract when given intravenously was fatal to most rabbits in thirty seconds to two minutes. Extracts of lung tissue of the guinea pig, sheep, dog and hog were essentially harmless to a rabbit, even when given in larger doses, but was fatal to the same species of animal. It was also observed that this curious action was highly specific for lung tissue only. Intravenous injection of large doses of homologous extracts of other organs, such as brain, liver, kidney, intestine and spleen, produced no untoward effects (Baker, Noran and Larson¹⁵).

It was discovered that the harmful effects of homologous lung extract could be prevented by a preliminary intravenous injection of 10 mg. of heparin, indicating that the reactions were due to some effect on the clotting mechanism. Lung tissue extract which had been heated at 56 C. for thirty minutes proved inactive, suggesting that the active principle within the lung tissue was thermolabile and probably contained thrombin.

It would appear, therefore, that in homogenizing lung tissue to prepare the extract thromboplastin was liberated. This substance would probably react with the prothrombin of the lung, causing the development of thrombin. This thrombin apparently is the active principle in the lung extract producing the precipitation of fibrin when inoculated

15. Baker, A. B.; Noran, H. H., and Larson, W. P.: Clotting of Blood in Vivo by Aqueous Homologous Lung Extract: Some Clinical Implications, *Proc. Soc. Exper. Biol. & Med.* **59**:196, 1945.

intravenously. From our studies, it would seem that in some cases of pneumonia the breakdown of the lung tissue results in a similar process, that is, in the liberation of thromboplastin, which initiates the mechanism of blood clotting, to result in plugs of fibrin within the cerebral vessels.

EXPERIMENTAL INVESTIGATION

METHOD

In order to throw further light on the morphologic character of the cerebral alterations associated with pneumonia, the brains of the experimental animals were studied pathologically. Thirty-one experimental animals, including rabbits, guinea pigs and dogs, were available. In many of the animals the tissue changes were necessarily acute, since the animals died immediately after inoculation with the lung extract. However, it was observed that smaller doses of the extract were frequently not fatal. Such sublethal inoculations were given to many animals in an attempt to produce a more chronic involvement of the brain. The response of the animals, however, was not consistent, since a few survived inoculation of as much as 1 cc. of the extract, while others died quickly after injection of as little as 0.25 cc. The brains of all the experimental animals were sectioned and prepared for microscopic study with the following staining technics: the routine phloxine-hematoxylin stain, the cresyl violet stain for Nissl bodies, the Weil stain for myelin sheaths, the Bodian stain for axis-cylinders, the Mallory-Heidenhain stain for connective tissue, the Alzheimer-Mann stain for astrocytes and the Mallory phosphotungstic acid hematoxylin stain. Nineteen of the experimental animals were rabbits, 5 were guinea pigs, and 7 were dogs.

RABBITS

The 19 rabbits were divided into four experimental groups. For the sake of convenience, these experiments were termed acute, subacute, subacute to chronic and chronic. A 1:25 saline dilution of extract of finely homogenized lung tissue from a rabbit was injected intravenously in all animals. In the acute experiments the animals died either immediately or within four or five hours after the inoculation of lung extract. When the animal lived more than one day or as long as two or three days, the experiment was arbitrarily termed subacute. All the rabbits of the subacute groups received two or more intravenous inoculations. In the subacute to chronic experiments the duration was six to twelve days. When several injections of the lung extract were given over a longer period, the experiment was regarded as chronic.

Acute Experiments.—Four rabbits were included in this study. Two had convulsions and died immediately after the intravenous inoculation of 1 cc. of homologous lung extract. Another animal survived a similar inoculation for five hours. The remaining animal survived an inoculation of 0.3 cc. Ten minutes later the rabbit was given an injection of 0.5 cc. One hour later, 1 cc. of lung extract was injected, and, although the animal's condition was critical, he survived. After three hours another inoculation of 1 cc. was given, followed immediately by convulsive seizures and death.

In all 4 animals the pathologic changes in the brain were essentially the same. In scattered areas there were sparse extravasations of red

blood cells into the subarachnoid space. An occasional perivascular space contained a small number of erythrocytes. Throughout the entire brain a large number of medium-sized and small vessels were partially to completely occluded with homogeneous eosinophilic material. In the case of the partially occluded vessels, this homogeneous material was observed only around the periphery of the lumen, leaving the central part of the lumen patent. Occasionally fine threads of fibrin could be seen with the routine stain. With Mallory's phosphotungstic acid hematoxylin stain, however, an interlacing network of fibrin was frequently observed within the homogeneous intravascular clot (fig. 1). In none of these animals were there any prominent alterations of the



Fig. 1.—Thin-walled vessel filled with a dense interlacing network of fibrin. Mallory's phosphotungstic acid hematoxylin stain.

neurons. Usually a few scattered nerve cells showed slight chromatolysis. The myelin sheaths revealed no evidence of abnormality.

Subacute Experiments.—Four rabbits were included in this group. All the animals received from two to four intravenous inoculations of lung extract over a period of two to three days. Three of the animals received intravenous injections of heparin prior to inoculation of 1 cc. of lung extract. The dose of heparin varied from 6 to 100 units. Twenty-five to 100 units seemed to afford the animal complete protection. Smaller doses often seemed to prevent immediate convulsions and death; this protection was not complete, since the animal frequently became extremely ill. In 1 case opisthotonos developed. About three

minutes later convulsive seizures occurred and the animal died. Another animal survived inoculation with 1 cc. of lung extract on two consecutive days. A similar dose of lung extract produced immediate convulsive seizures and death on the third day.

The microscopic changes observed in the brain were identical in all animals and were very similar to those in the preceding group. Small extravasations of red blood cells were usually seen in the sub-arachnoid space and in a few scattered perivascular spaces within the parenchyma of the brain. The lumens of many of the cerebral vessels were partially to completely obstructed with homogeneous clots (fig. 2), in which Mallory's stain revealed numerous threads of fibrin, often arranged as a rather dense interlacing network. The nerve cells

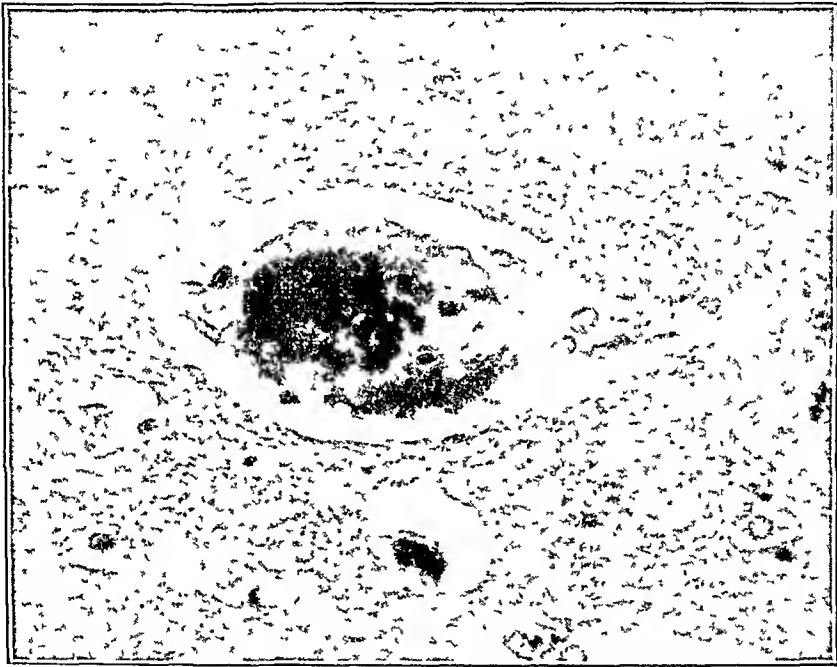


Fig. 2.—A small vessel partially occluded with a homogeneous clot. The central part of the lumen is still patent. Hematoxylin-eosin stain.

presented somewhat more prominent alterations. The cresyl violet stain revealed some chromatolysis. A rather large number of ganglion cells showed evidence of early shrinkage and pyknosis. The Weil stain demonstrated scattered areas of early perivascular degeneration of myelin. In a few places actual beginning fragmentation of the myelin sheaths was observed.

Subacute to Chronic Experiments.—Four rabbits comprised this group. The experiments extended over a period varying from six to twelve days. One animal received inoculations of 0.3, 0.5 and 0.75 cc. of lung extract intravenously at fifteen to thirty minute intervals. The

animal survived six days but later had convulsions and died after an inoculation of 0.3 cc. The other 3 rabbits received two injections of 1 cc. of the lung extract. Two died during convulsive seizures. The remaining animal exhibited paralysis of both hindlegs and urinary retention after the second intravenous injection. The animal was killed eight days later.

The pathologic changes observed in the brain were very similar to those in the preceding group. In all the brains, scattered vessels were partially to completely filled with homogeneous clots. Mallory's phosphotungstic acid hematoxylin stain revealed many of the clots to be composed largely of fibrin. In some vessels the strands of fibrin were very coarse and at times were fused into a solid mass. An occasional tiny perivascular extravasation of erythrocytes was observed. There were also disseminated areas of mild hemorrhage into the subarachnoid space. In 1 case the perivascular hemorrhages were most numerous in the cerebellum. Alterations of the nerve cells were relatively mild. Some neurons were pale, swollen and chromatolytic, while others were somewhat shrunken and hyperchromatic. Only mild alterations of the myelin sheaths had occurred, and those in widely separated areas of the brain.

Changes in the brain were relatively mild in the animal in which paralysis of the posterior limbs had developed. In this case the alterations in the spinal cord were more striking. Small perivascular hemorrhages were disseminated throughout the anterior horns of the cord. The anterior horn cells showed rather prominent alterations, similar to those occurring in the brain. Throughout the white matter of the cord much of the myelin was swollen and rarefied. In some areas there was actual beginning vacuolation of the myelin sheath. These alterations were best demonstrated by the Weil stain. In the vicinity of the central gray matter of the cord, an occasional capillary contained a clot similar to those observed in the brain.

Chronic Experiments.—There were 6 rabbits in this group. Three to thirteen intravenous injections of the lung extract were given over a period varying from two to eleven weeks. The sublethal inoculations ranged from 0.3 to 1 cc. of the extract. In only 1 case was heparin administered prior to the lung extract.

In 5 animals the pathologic changes in the brain were somewhat similar to those described in the preceding groups. In the 2 remaining animals somewhat different observations were observed. A case illustrative of each group will be described:

ANIMAL 3.—This rabbit received intravenous inoculations of 1 cc. of the homogenized saline extract at weekly intervals. The animal became slightly ill after the first two inoculations but survived. After the third injection convulsive seizures promptly appeared and resulted in death.

The external surface of the brain revealed rather prominent vascular congestion with scattered small areas of subarachnoid bleeding. Coronal sections of the brain demonstrated nothing of significance except for vascular congestion.

Microscopic study with the routine phloxine-hematoxylin stain revealed that scattered vessels throughout the brain contained homogeneous eosinophilic material. In many of the vessels this structureless material filled essentially the entire lumen (fig. 3). Occasionally fine threads of fibrin could be made out, suggesting that these intravascular structures were either clots or thrombi. With Mallory's phosphotungstic acid hematoxylin stain these lesions were frequently observed to consist of a dense intertwining network of fibrin. In longitudinal sections of the vessels long segments were seen to be filled with long threads of fibrin (fig. 4 *A*). The smaller vessels, including the capillaries, were most frequently involved. Relatively large vessels, however, were also occluded with the same homogeneous material, which with special stains was seen to contain a dense network of fibrin

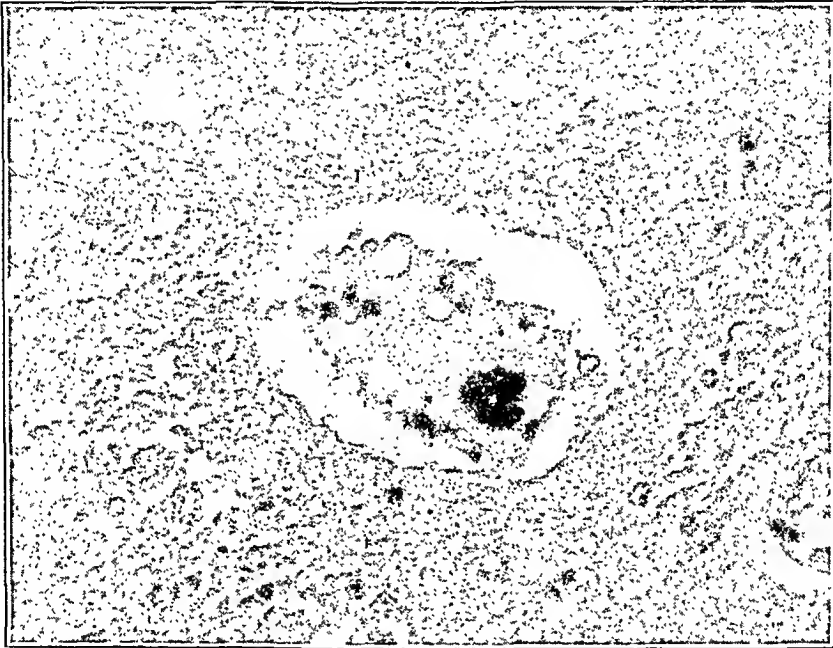


Fig. 3.—A small vein filled with homogeneous material resembling a clot. Only a few clumps of red cells are observed. Phloxine-hematoxylin stain.

(fig. 4 *B*). Some of the larger vessels in the choroid plexus were involved. Occasional vessels were filled with a pale yellow material, which contained little or no fibrin. The impression was that this structureless material consisted of serum adjacent to a contracted intravascular clot. Longitudinal sections of certain vessels demonstrated elongated clots, which had shrunk and contracted away from certain parts of the wall. There were a few scattered perivascular hemorrhages, together with slight extravasations of blood into the subarachnoid space.

The Nissl stain brought out alterations in a large percentage of the nerve cells throughout most of the brain. Throughout the cerebral cortex many neurons showed definite shrinkage and pyknosis, with some deformity of the cell body and its processes (fig. 5). Other cortical neurons showed prominent chromatolysis, which was often associated with paling of the cell nucleus (fig. 5). The cytoplasm of an occasional cell contained a few tiny vacuoles. A few ghost cells were seen in

scattered regions. There were occasional disseminated small foci of very early demyelination. These lesions were usually perivascular and were most numerous within the white matter of the cerebrum (fig. 6 *A*). In some regions degeneration of myelin was more diffuse. In the earliest stage of involvement the myelin

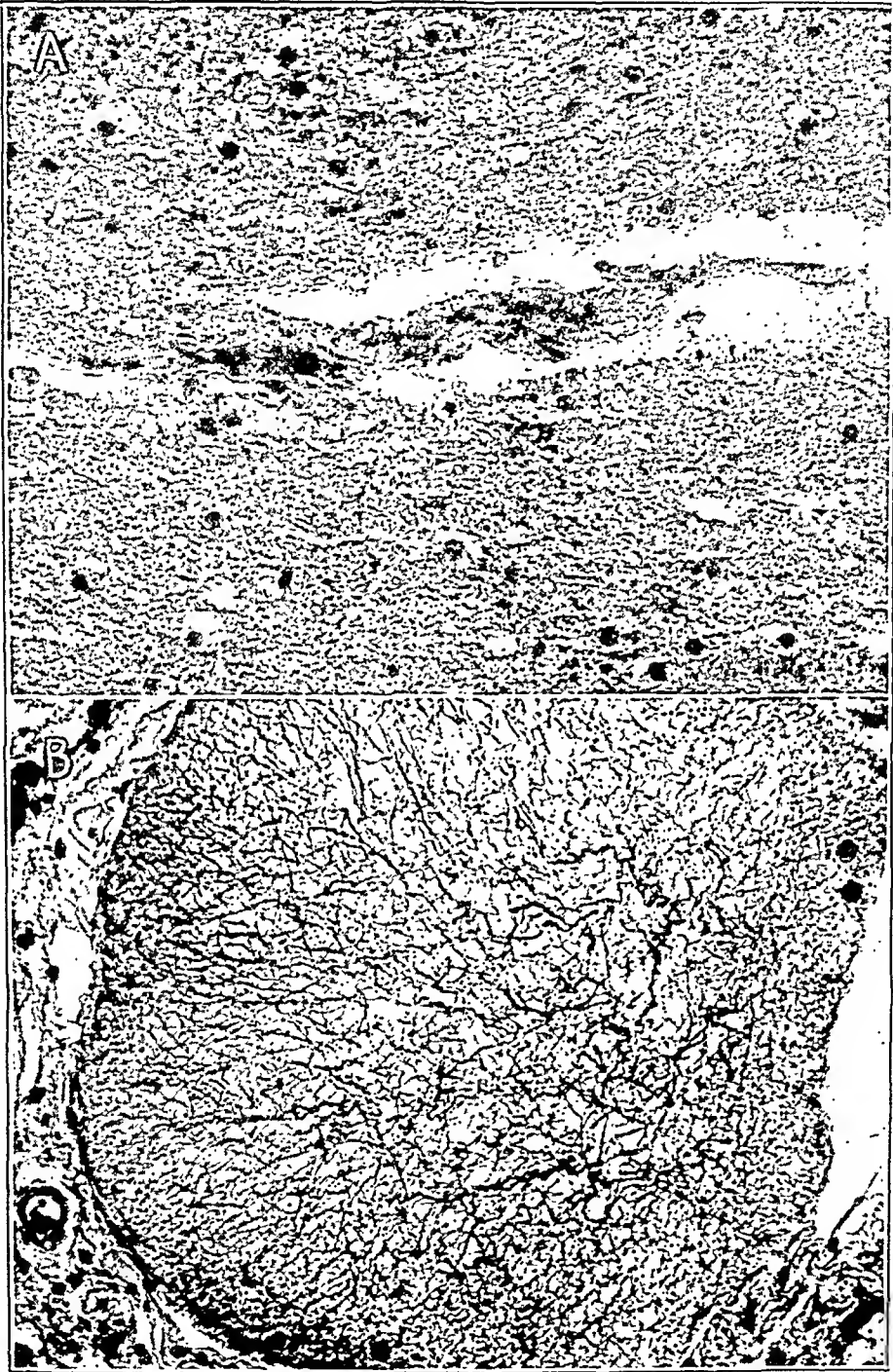


Fig. 4.—*A*, longitudinal section of a small cerebral vessel, showing long strands of fibrin filling the lumen of the vessel. *B*, lumen of a rather large vessel filled with a prominent network of fibrin. Mallory's phosphotungstic acid hematoxylin stain.

sheaths were merely slightly swollen and pale. In the more advanced lesion the Weil stain showed mild, but more definite, perivascular rarefaction of the myelin.

The neuropathologic alterations observed in this brain were similar to those noted in the brains of the other 4 rabbits of this group.

ANIMAL 29.—This rabbit became acutely ill after an intravenous injection of 1 cc. of the lung extract. The rabbit survived, however, without any apparent residual neurologic disturbance. The animal was then given injections of 0.3 cc. of the extract on five different occasions at intervals varying from five days to three weeks. The animal survived these inoculations, but six weeks later fatal convulsions followed another intravenous injection of 0.3 cc. of the extract.

Grossly, the brain showed prominent congestion and small subarachnoid extravasations of blood. Microscopic study demonstrated numerous intravascular clots similar to those previously described. There were also occasional small perivascular hemorrhages. Another type of involvement was frequently noted in the walls of vessels. This was evidenced by swelling and proliferation of the endothelial lining of the vessel, producing attenuation of the lumen. In scattered vessels polymor-

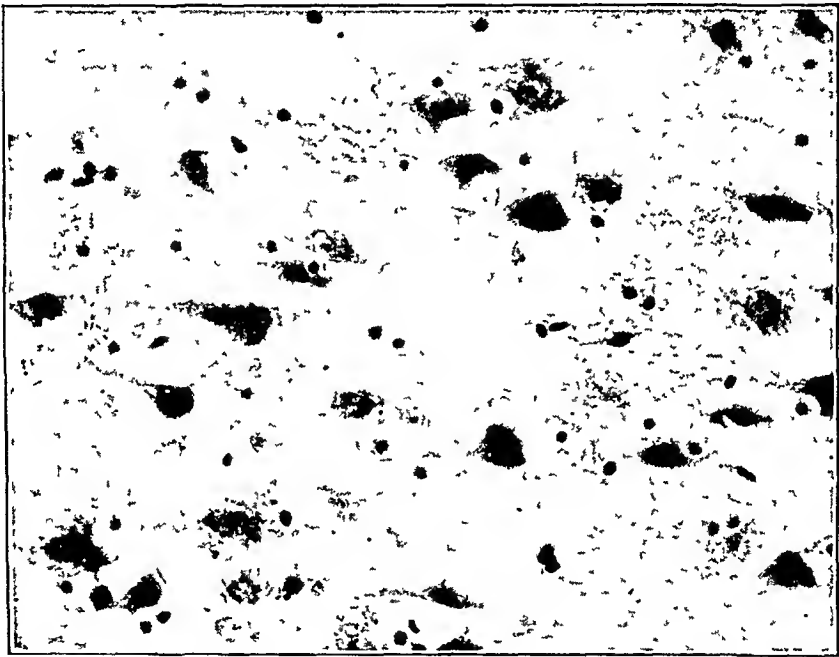


Fig. 5.—Cerebral cortex, showing shrinkage and pyknosis of many neurons. Others have become pale and lost most of their internal structure. Note the occasional ghost cell. Cresyl violet stain.

phonuclear leukocytes had infiltrated the walls of the vessels. Occasionally leukocytes invaded the perivascular spaces, resulting in small focal collections of neutrophils. In irregularly scattered regions a sparse invasion of the leptomeninges with polymorphonuclear leukocytes was observed. Throughout the brain alterations in the nerve cell were encountered similar to those already described except that they were much severer. There were also perivascular and diffuse areas of degeneration of myelin. The alterations in the myelin were also similar but were more prominent and severer.

GUINEA PIGS

There were 5 animals in this group. All were given intracardiac injections of 1 cc. of a homologous lung extract. Two to three inocula-

tions were performed, at intervals of one day, in each case. Four of the animals died during the convulsive seizure that followed the final inoculation. The remaining animal survived the convulsive seizure but died the next day.

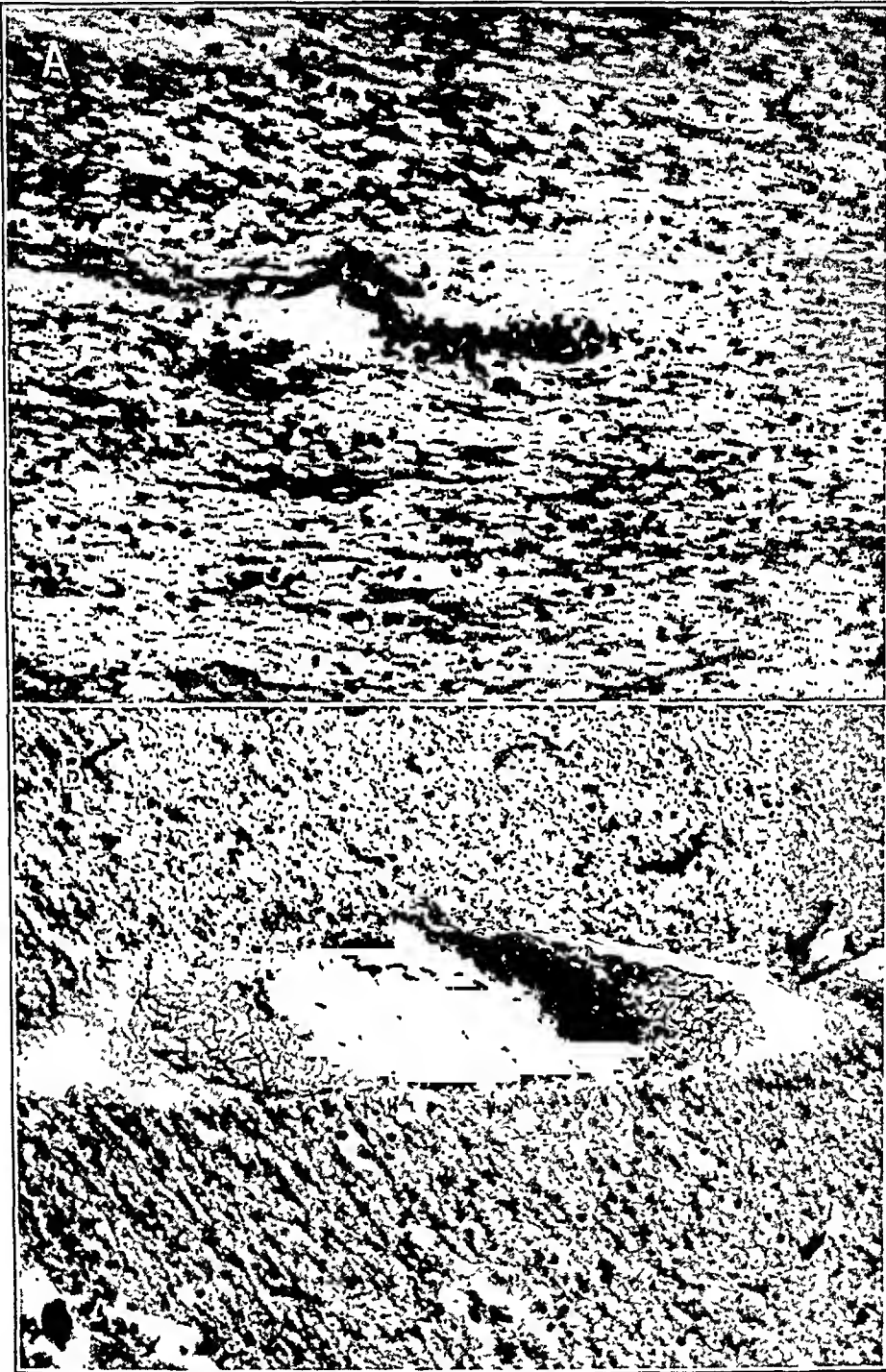


Fig. 6.—*A*, early perivascular demyelination, with partial loss of the tinctorial property of the myelin encircling the vessel; Weil's myelin sheath stain. *B*; peripheral zone of the lumen of the vessel occluded with a fibrin clot; Mallory's phosphotungstic acid hematoxylin stain.

In all 5 animals the brain showed a very similar type of pathologic alteration. Gross examination demonstrated moderate vascular con-

gestion. The microscopic observations were nearly the same as those described in the rabbits. Minute perivascular extravasations of blood were observed disseminated irregularly throughout the cerebral cortex. Numerous small vessels were partially to completely occluded with homogeneous clots, which with the Mallory phosphotungstic acid hematoxylin stain were seen to contain numerous threads of fibrin (fig. 6 *B*). In all animals there were rather prominent shrinkage and pyknosis of the neuron cells. The Weil stain revealed irregular areas in which the myelin was becoming pale. In 1 brain a sparse infiltration of polymorphonuclear leukocytes was observed around the adventitia of a few of the occluded vessels.

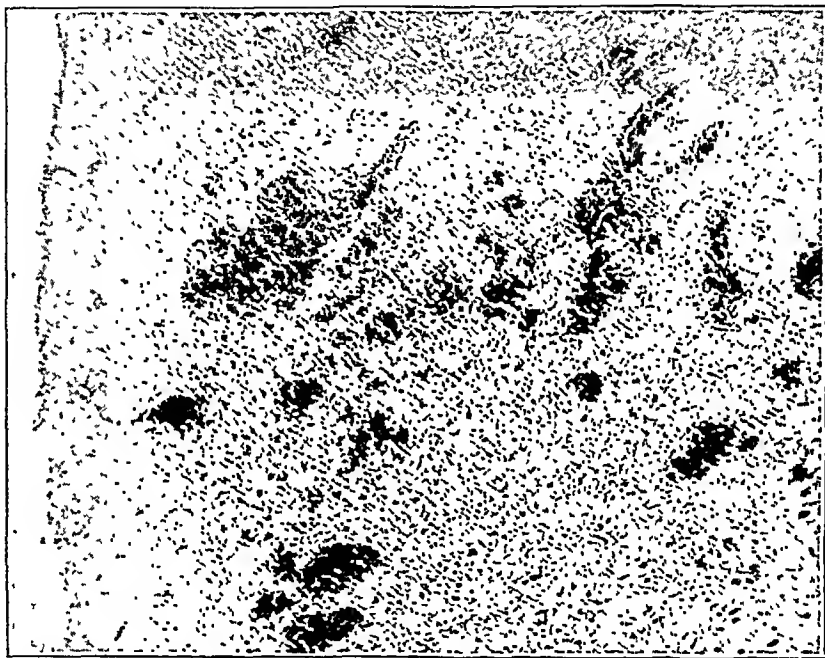


Fig. 7.—Prominent petechiae disseminated through the cortex; phloxine-hematoxylin stain.

DOGS

There were 7 dogs in this group.

One dog was given 20 cc. of homologous lung extract intravenously on two occasions, one week apart. After the first inoculation convulsive seizures developed. The animal survived but remained confused. At the time of the second inoculation the dog had not completely recovered. After the second injection another convulsive seizure developed. After remaining comatose for about one hour, the animal died.

Microscopic examination revealed petechial hemorrhages scattered throughout the brain. In certain areas of the cerebral cortex these petechiae were quite prominent (fig. 7). The hemorrhages generally consisted in an extravasation of the red blood cells into the perivascular spaces. Occasionally the bleeding actually extended into the surrounding cerebral parenchyma for a short distance. There

were no large hemorrhages. Throughout the entire brain the vessels were partially to completely filled with structureless material identical with that observed in the rabbits and the guinea pigs. These intravascular clots were somewhat more numerous in the gray matter but were also prominent in the white matter. The

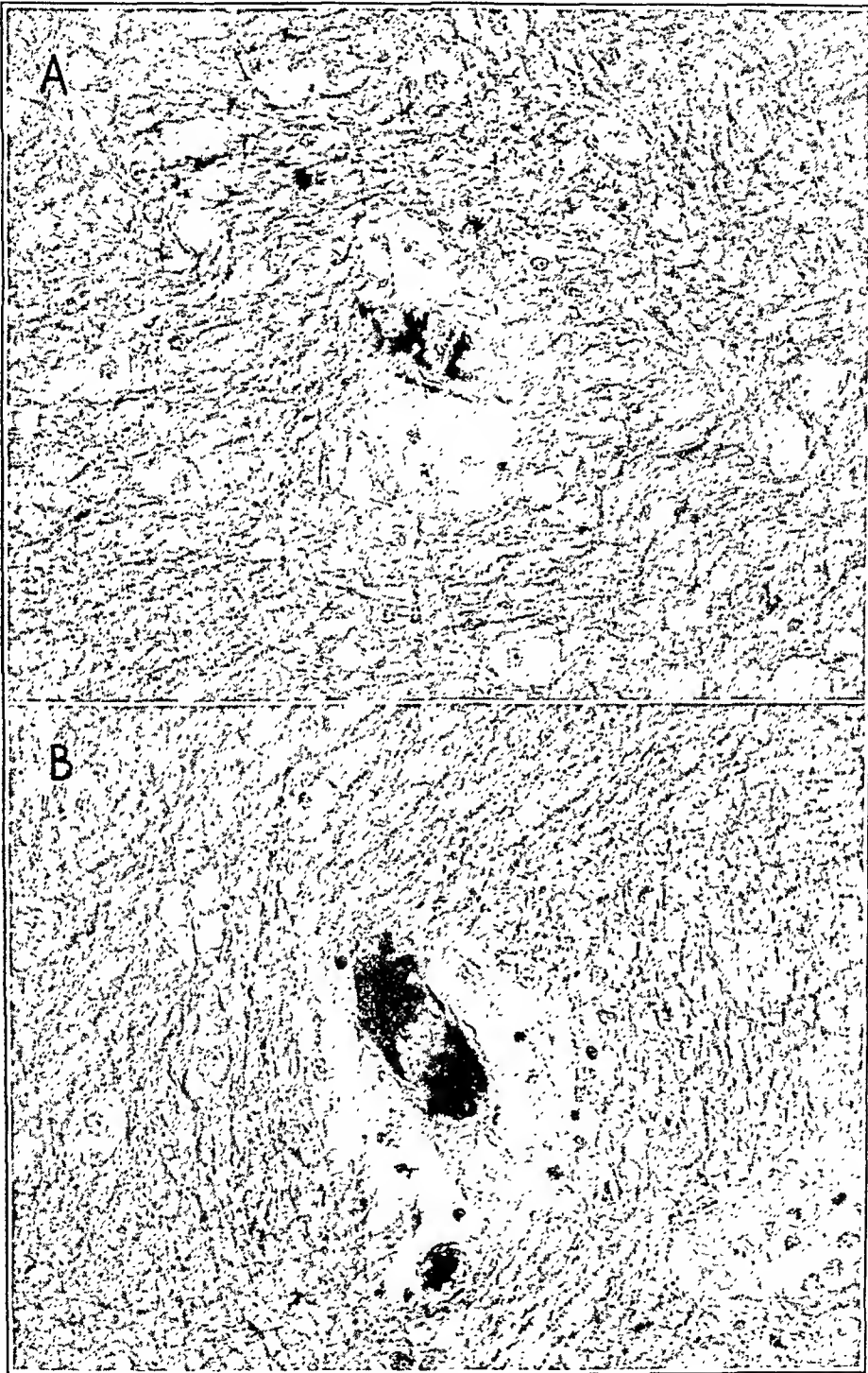


Fig. 8.—*A*, lumen of a tiny vessel containing very coarse strands of fibrin. *B*, coarse fibrin within the vessel fused into an almost solid mass. Mallory's phosphotungstic acid hematoxylin stain.

smaller vessels frequently contained irregular strands of fibrin (fig. 8 *A*). These were visible only with Mallory's phosphotungstic acid hematoxylin stain. In some

of the vessels the fibrin was very coarse and was frequently fused into a relatively solid mass (fig. 8 *B*). Throughout the brain there were prominent shrinkage and pyknosis of a large number of the ganglion cells. The myelin sheaths showed early irregular degeneration. This alteration in myelin tended to occur in regions where the intravascular clots were most numerous.

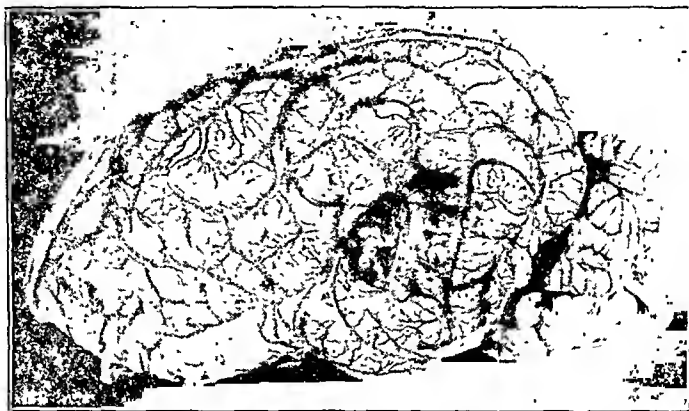


Fig. 9.—Vascular congestion and scattered punctate hemorrhages visible on the surface of the brain.



Fig. 10.—Lumen of a vessel filled with needles and threads of fibrin. Mallory's phosphotungstic acid hematoxylin stain.

In the remaining 6 dogs, the homologous lung extract was injected into the carotid artery. Inoculations, ranging from 2 to 5 cc., were given at intervals of one week. Three animals received three injec-

tions and the other 3 four injections. All the animals died in a convulsive seizure after the final inoculation, of 5 cc., of the extract.

The morphologic changes observed in the brain were similar in all the animals.

ANIMAL 52.—The brain of this dog will be described, since it revealed somewhat more striking hemorrhagic lesions than the others. Gross examination revealed a small amount of subarachnoid bleeding along some of the cerebral sulci. The entire surface of the brain was moderately congested. In a few areas there were small focal hemorrhages within the cerebral cortex. These could be seen on external inspection of the brain (fig. 9). Sparse subarachnoid hemorrhages, scattered perivascular hemorrhages and numerous intravascular clots were the outstanding microscopic observations. Mallory's phosphotungstic acid hematoxylin stain demonstrated interlacing threads of fibrin within the intravascular clots, even though they appeared structureless with the routine stain (fig. 10). Both the large and the small vessels were partially to completely occluded with these clots. Even with the Nissl stain, only mild alterations of the cerebral neurons were observed. With special staining, the myelin sheaths showed little evidence of degeneration.

In the other 5 dogs the hemorrhagic lesions in the brain were not so prominent; otherwise, the microscopic observations were essentially similar to those just described.

COMMENT

The striking observation in this series of experiments was the consistent and uniform pathologic alteration present in the brain. In all the animals numerous intravascular clots partially to completely occluded the lumens of many vessels. With the routine stain these clots appeared to be structureless and homogeneous, but with Mallory's phosphotungstic acid hematoxylin stain they were seen to contain numerous interlacing threads of fibrin. This fibrin was occasionally so coarse and dense that it was fused into almost solid masses. The earliest clotting occupied only the periphery of the vascular lumen, leaving the central part of the lumen patent. In occasional vessels structureless material, devoid of fibrin, filled the lumen. This seemed to represent serum adjacent to areas where the fibrin had contracted into a smaller mass.

In all the animals there were variable numbers of scattered petechial cerebral hemorrhages, as well as irregular areas of subarachnoid bleeding. The petechial hemorrhages tended to be more prominent in the dogs than in the rabbits or the guinea pigs. These hemorrhagic lesions were not so prominent or so consistent as the vascular clots. The latter seemed to be the more basic and fundamental manifestation of the pathologic process and probably gave rise to the vascular bleeding.

In 2 of the chronic rabbit preparations there were multiple perivascular inflammatory reactions, suggesting early abscess formation.

Intravascular clotting was prominent throughout both brains. There were rather advanced degenerative changes in the cerebral parenchyma secondary to the vascular occlusions, strongly suggesting that the vascular inflammation was a reaction to the destruction of tissue. Nevertheless, the suppurative nature of the inflammatory infiltrate makes it necessary for one to consider the possibility of the introduction of an infectious agent during the inoculations. Until further investigation is carried out, observations on these 2 rabbits cannot be adequately evaluated.

Except in these 2 rabbits, the cerebral parenchyma revealed only mild alterations. The neurons often showed swelling and chromatolysis. In the more chronic preparations they frequently also exhibited ischemic changes, such as shrinkage and pyknosis. The myelin sheaths of the nerve fibers were usually intact, with only mild alterations in occasional perivascular zones. In the longer experiments diffuse changes in the myelin were observed, in addition to the perivascular degeneration. There was no actual destruction of axons.

Comparison with the morphologic alterations observed in the human nervous system in cases of "pneumonic encephalitis" will show that the experimental lesions and those in the human brain are essentially identical. This suggests that both are the result of the same process, namely, the introduction of some product from the lung into the blood stream which facilitates blood clotting. These pathologic observations are additional proof that the cerebral complications of pneumonia may result from a disturbance of the clotting mechanism. This experimental reproduction of the lesions of so-called pneumonic encephalitis clearly indicates that pneumonitis liberates some product from the patient's lung which, in turn, produces an intravascular clotting in the cerebral vessels.

When one considers the frequency of infections of the respiratory tract and the possibility that a patient may be affected by a breakdown of his own lung tissue, it becomes apparent that this phenomenon may have implications of significance in other conditions—especially those in which clots or thrombi have been observed within the vessels of the nervous system. Such vascular lesions have been observed in association with a number of the encephalitides and with some of the degenerative maladies of the nervous system. Putnam and Alexander¹⁶ recognized vascular thrombi within the brain in 3 cases of encephalitis after measles and in 2 cases of encephalitis after antirabies vaccination. Ferraro and Scheffer¹⁷ noted venous thrombi associated with

16. Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, *Arch. Neurol. & Psychiat.* **41**:1087 (June) 1939.

17. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles, *Arch. Neurol. & Psychiat.* **25**:748 (April) 1931.

encephalitis that followed measles. Scheinker¹⁸ observed intravascular clots, which he regarded as part of his concept of "vasoparalysis and vasothrombosis," in 3 cases in which the etiologic factor was not clear. It is interesting to note that pneumonia was also present in 1 case.

In the numerous reports of postinfectious and secondary forms of encephalitis almost no mention is made of vascular clots or thrombi. It is possible that the small intravascular clots may have been overlooked or were not mentioned because they were regarded merely as a postmortem process, of no pathologic significance. This tendency to disregard these intravascular clots was experienced by us in our early cases of "pneumonia encephalitis," until we became aware of the consistency of their occurrence in a series of cases and observed that they were always present even when the hemorrhagic lesions were relatively inconspicuous. Putnam¹⁹ noted thrombi in all his 3 cases of encephalomyelitis of undetermined cause.

For many years Putnam has been the chief exponent of the clotting theory of multiple sclerosis. He observed clots in the cerebral veins in 9 out of 17 cases of multiple sclerosis. Recently he has reduced the number of exacerbations in cases of disseminated sclerosis by giving "dicumarol" over a period (Putnam²⁰). Because no changes were noted in the walls of the cerebral vessels, he postulated that the cause of the clotting or thrombosis must be in the circulating blood. Dawson,²¹ who also observed thrombi in cases of multiple sclerosis, noted the normalcy of the walls of the involved vessels and the absence of the expected organization of the clots. We should like to point out that involvement and breakdown of the lung tissue has not been excluded in any of the aforementioned conditions. We suggest that this ability of the patient's own lung tissue to produce intracerebral clotting be given more consideration, since it may play a role in many neurologic diseases, and even in some of the obscure psychiatric conditions. An example of the latter are the behavior disorders following infections of the respiratory tract in which definite pneumonia is not present (Richter²²).

18. Scheinker, I. M.: Vasoparalysis and Vasothrombosis of the Brain in Infancy and in Early Childhood, *Arch. Neurol. & Psychiat.* **55**:216 (March) 1946.

19. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," *Arch. Neurol. & Psychiat.* **37**:1298 (June) 1937.

20. Putnam, T. J.: The Use of Dicoumarin in the Treatment of Multiple Sclerosis, *Tr. Am. Neurol. A.*, 1946, p. 26.

21. Dawson, J. W.: The Histology of Disseminated Sclerosis, *Tr. Roy. Soc. Edinburgh* **50**:517, 1916.

22. Richter, H. G.: Emotional Disturbances of Constant Pattern Following Nonspecific Respiratory Infections, *J. Pediat.* **23**:315, 1943.

Two interesting experiments should be mentioned in this discussion. The first, performed by Hoefer, Putnam and Gray,²³ was similar to ours in that these investigators were able to produce thrombi in the various organs, including the brain, of experimental animals by injecting lung and brain extracts. The type of reaction we obtained in our animals could not be produced with brain extract. From their report, one cannot determine whether they used homologous or heterologous extracts of the organs. In the second experiment, performed by Ferraro,²⁴ the results suggested to him an allergic basis for postinfectious encephalitides and degenerative neurologic conditions, such as multiple sclerosis. He made monkeys sensitive to either egg white or rabbit brain extract. These substances were then inoculated intracerebrally into the sensitized animals. Cerebral edema, petechiae, perivascular collections of microglial elements and leukocytes, parenchymal changes and thrombosis of small vessels resulted. It is difficult to apply the results of this experiment to human cases, since the brain extract was not from the same species of animal. Also, the antigen-antibody theory would not explain the immediate fatal convulsive seizures following the inoculations of homologous lung extract in an unsensitized animal.

In concluding this discussion, it is important to mention that the intravascular clots, produced by the breakdown of lung tissue in cases of pneumonitis or by the inoculation of homologous lung extract, differ from the usual thrombi. In the case of intravascular clotting the wall of the vessel, including the intima, is intact. The usual clumps and masses of platelets, so typical of thrombi, are not seen, except in the clots occluding the larger vessels. Instead of large numbers of platelets adhering to a roughened area of the intimal lining of the vessel, a dense network of fibrin forms within the lumen of the vessel to produce an intravascular clot. The process is similar to the experimental clotting produced by clotting agents within a test tube in the laboratory. We feel, therefore, that we are justified in concluding that the phenomenon is a true intravascular clotting which differs from thrombosis.

SUMMARY

The literature on the clinical and pathologic features of the cerebral complications of pneumonia is briefly reviewed.

Homologous lung extract was injected into 31 experimental animals. Most of the animals died in convulsive seizures after the last inoculation. Other organs or lung tissue from a heterologous species failed to produce a similar reaction.

23. Hoefer, P. F.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injections of Various Coagulants, *Arch. Neurol. & Psychiat.* **39**:799 (April) 1938.

24. Ferraro, A.: Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain, *Arch. Neurol. & Psychiat.* **52**:443 (Dec.) 1944.

The brains of the experimental animals showed pathologic changes identical with those observed in cases of so-called pneumonic encephalitis in man. The fundamental lesion was a diffuse intravascular clotting. These clots differ from thrombi in that they consist of a homogeneous material in which special stains reveal a dense network of fibrin. The walls of the involved vessels are normal, and masses of platelets are rarely seen.

This study offers further proof that the encephalic complications of pneumonia are the result of an intravascular clotting. This clotting reaction is apparently set off by some product which is liberated from the lung during the pneumonitis.

The widespread frequency of infections of the respiratory tract and the possibility that a breakdown of the patient's tissue may produce intravascular clotting make it necessary to consider such a process in many conditions of unknown cause in which thrombi have been observed.

University of Minnesota Medical School.

BALLISM AND THE SUBTHALAMIC NUCLEUS (NUCLEUS HYPOTHALAMICUS; CORPUS LUYSI)

Review of the Literature and Study of Thirty Cases

J. R. WHITTIER, M.D.

NEW YORK

I. GENERAL CONSIDERATIONS

Historical Development of Hemiballism.—"Hemiballism" became associated with pathologic changes in the subthalamic nucleus (nucleus hypothalamicus; corpus Luysi) during the decade following 1920 (Jakob,¹ Martin,² von Sántha³ and Matzdorff⁴).

That involuntary movements sometimes appeared after lesions localized in various parts of the brain had long been known. Weir Mitchell⁵ and Charcot⁶ recognized their frequent unilateral occurrence after apoplexies with the terms "posthemiplegic chorea" and "hemichorea." These terms, with the earlier contribution of "athetosis" by Hammond,⁷ generally sufficed to distinguish the types of movements encountered.⁸

This study was aided by a grant from the William J. Matheson Commission. From the Department of Neurology, Columbia University College of Physicians and Surgeons.

1. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923, p. 328.

2. Martin, J. P.: Hemichorea Resulting from a Local Lesion of the Brain (Syndrome of the Body of Luys), *Brain* **50**:637-651, 1927.

3. von Sántha, K.: Zur Klinik und Anatomie des Hemiballismus, *Arch. f. Psychiat.* **84**:664-678, 1928.

4. Matzdorff, P.: Beiträge zur Pathologie des extrapyramidal-motorischen Systems; das Syndrom des Corpus Luysi, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **109**:538-554, 1927.

5. Mitchell, S. W.: Post-Paralytic Chorea, *Am. J. M. Sc.* **68**:342-352, 1874.

6. Charcot, J. M.: *Lectures on the Diseases of the Nervous System*, translated by G. Sigerson, Philadelphia, Henry C. Lea, 1879, p. 214.

7. Hammond, W. A.: *A Treatise on Diseases of the Nervous System*, ed. 1, New York, D. Appleton and Company, 1871, p. 654.

8. Gowers (On Athetosis and Post-Hemiplegic Disorders of Movement, *Med.-Chir. Tr.*, London **59**:271-325, 1876) disapproved of the terminology, not without foresight. In 1876 he wrote (page 277): "I have preferred not to use the term 'post-hemiplegic chorea' in speaking of any of these cases for two reasons: First, I think the term tends to confuse together several easily distinguishable varieties of movements, which may ultimately be found to depend upon pathological processes of different kinds or in different localities; secondly, the word chorea . . . were better not transferred to a symptom."

In the German literature, the flinging or throwing of the limbs arising from violent involvement of proximal musculature was described under the term "hemiballismus." Thus, Greidenberg⁹ commented:

The most frequent form of posthemiplegic motor disturbance, and hence the most adequately investigated, is without doubt hemichorea (posthemiplegic or post-apoplectic hemichorea, *hemichorée posthémiplégique* [Charcot], hemikinesia [Hughlings Jackson], hemiballismus [Kussmaul]).

He described a case (without autopsy) in which this violent and flinging type of movement occurred unilaterally and referred to it as one of "typical hemichorea." Von Monakow¹⁰ described the symptom as follows:

Posthemiplegic chorea (hemiballismus of Kussmaul^[11]) is characterized by a profusion of vigorous involuntary movements, sometimes rhythmic, at other times irregular, appearing in the hemiplegic limbs, especially in the arms and less frequently in the legs. The entire limb is affected . . . and (the movements) appear most often in the form of a flinging spasm (hemiballismus).

He noted that the symptom occurred with softenings and tumors, as well as with hemorrhages, and that it tended to appear when the lesion was in the posterior part of the thalamus or in the lenticulo-optic area.

With regard to the particular site of lesions evoking the symptom, Bonhoeffer¹² remarked, in his discussion on the *Bindarmtheorie*, that "the subthalamic region in the optic thalamus is observed to be involved in the majority of lesions in question." Touche,¹³ describing unequivocal hemiballism in his case of "hemichorea," and observing that a hemorrhage completely masked the subthalamic nucleus, commented: "One might ask oneself whether the violence of the movements was not due specifically to the lesion of the body of Luys."¹⁴

9. Greidenberg, B.: Ueber die posthemiplegischen Bewegungsstörungen, Arch. f. Psychiat. **17**:9-216, 1886.

10. von Monakow, C.: Gehirnpathologie, Vienna, A. Hölder, 1897, p. 318.

11. The suffix "-us" is a relic of little value from days when it was appended to many words, including "hypnotismus" and "somniaambulismus"; and it may be conveniently dropped. References for Kussmaul's coining of "hemiballismus" were not cited by Greidenberg, von Monakow or subsequent writers, e. g., H. Oppenheim (Lehrbuch der Nervenkrankheiten für Aerzte und Studierende, ed. 4, Berlin, S. Karger, 1905, p. 699), Jakob¹ and Herz.²¹ As was found by Moersch and Kernohan,²⁴ search for the term in Kussmaul's published works is unrewarding. The word "ballismus" comes through the Latin *ballista*, from the Greek *βάλλειν*, meaning "to throw."

12. Bonhoeffer, K.: Ein Beitrag zur Localisation der choreatischen Bewegungen, Monatschr. f. Psychiat. u. Neurol. **1**:6-41, 1897.

13. Touche: Deux cas d'hémichorée organique avec autopsie, Rev. neurol. **9**: 1080-1081, 1901.

14. The subthalamic nucleus (nucleus hypothalamicus), recognized by Luys (Recherches sur le système nerveux cérébro-spinal, Paris, J.-B. Baillière et fils, 1865, pp. 143-144) and described in detail by Forel (Untersuchungen über die Haubenregion und ihre oberen Verknüpfungen im Gehirn des Menschen und

Without using the term hemiballism, von Economo¹⁵ described a case of posthemiplegic hemichorea of an especially violent nature, with a lesion in the contralateral subthalamic nucleus. Fischer,¹⁶ calling the symptom "hemiballismus," described a similar lesion in case 5 of his series. It remained only for A. Jakob¹ to combine the picture in his case of "hemiballismus" (case 19, page 174) with the observations of von Economo and Fischer and establish the "syndrome of the corpus Luysi," which he described as follows:

. . . The syndrome is a peculiar contralateral disturbance of movement which usually bears a similarity to choreiform movements of stormy nature, but surpasses by far the ordinary manifestations of chorea. It appears as irregular and incoordinated contorting movements of the muscle masses of an entire half of the body, with a pronounced tendency to attacks of twisting and turning. The symptom is called hemiballismus.

Authors since Jakob have emphasized the movements of the limbs more than those of the trunk. Jakob mentioned also that von Economo informed him orally that in the latter's case of 1910¹⁵ the condition, reported as "hemichorea," had been "wholly typical hemiballismus."

TABLE 1.—*Chronology of Thirty Reported Cases of Hemiballism Occurring with Localized Lesions of the Subthalamic Nucleus*

Decade.....	1880-1889	1890-1899	1900-1909	1910-1919	1920-1929	1930-1939	1940-1947
No. of cases...	2	0	1	3	8	14	2

By 1930 the frequent appearance of hemiballism contralateral to a lesion of the subthalamic nucleus had become fairly well established (table 1).

Relation of Ballism to Chorea.—Whether the symptom of hemiballism can be distinguished from other patterns of involuntary movement has been the subject of much controversy. Wilson¹⁷ did not

einiger Säugetiere, mit Beiträgen zu den Methoden der Gehirnuntersuchung, Arch. f. Psychiat. 7:393-495, 1877), is roughly a lens-shaped structure situated on the fibers of the internal capsule as they pass ventrocaudad at the level of the mamillary bodies. What is known concerning its anatomy and connections was summarized by Sano (Beitrag zur vergleichenden Anatomie der Substantia nigra, des Corpus Luysii und der Zona incerta, Monatschr. f. Psychiat. u. Neurol. 27: 110-127, 1910 [subthalamic nucleus, pp. 114-117]) and Ariëns Kappers, Huber and Crosby (The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936, vol. 2, pp. 1174-1175).

15. von Economo, C. J.: Beitrag zur Kasuistik und zur Erklärung der posthemiplegischen Chorea, Wien. klin. Wchnschr. 23:429-431, 1910.

16. Fischer, O.: Zur Frage der anatomischen Grundlage der Athetose double und der posthemiplegischen Bewegungsstörung überhaupt, Ztschr. f. d. ges. Neurol. u. Psychiat. 7:463-486, 1911.

17. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940.

use the term hemiballism and stated only that "vascular and other lesions in various cerebello-mesencephalo-strio-thalamo-cortical fields can induce chronic choreas." Jelliffe and White¹⁸ did not mention the subject, but the majority of authors of textbooks describe the symptom briefly and ascribe it to lesions of the contralateral subthalamic nucleus. The *Quarterly Cumulative Index Medicus* lists cases of hemiballism under headings of "chorea," "athetosis" and "spasm."

Martin¹⁹ denied that a differentiation of hemiballism from other choreas was justified except on the basis of quantitative aspects of the movements. Wenderowic,²⁰ arguing "non sunt multiplicanda entia sine necessitate," affirmed the existence of a quantitative difference, susceptible only to "intuitive" analysis. Herz,²¹ after motion picture studies of a variety of involuntary movements, including 2 cases of ballism (without autopsy), suggested that the mechanisms of chorea were not completely identical with those of ballism.

Van Sántha³ and Balthasar²² spoke for a clear differentiation of hemiballism from other choreas on the basis of form or pattern of the movements, and Davison and Goodhart,²³ expressing agreement with these authors, asserted that the pattern depended on which structure was involved and that ballism appeared only when the subthalamic nucleus was destroyed. Moersch and Kernohan²⁴ noted that the terms hemichorea and hemiballism were used interchangeably, but reserved hemiballism for the hemichorea of elderly patients, making their distinction not on the pattern of the movements but on the incidence, onset, course and similar features. Bucy²⁵ stated that "the definition of hemiballismus rests primarily upon the pathology and not upon the clinical features." Keschner²⁶ protested that "although

18. Jelliffe, S. E., and White, W. W.: Diseases of the Nervous System, ed. 6, Philadelphia, Lea & Febiger, 1935.

19. (a) Martin.² (b) Martin, J. P., and Alcock, N. S.: Hemichorea Associated with Lesions of the Corpus Luysi, *Brain* **57**:504-516, 1934.

20. Wenderowic, E.: Ueber das anatomische Substrat des Hemiballismus bzw. der Hemichorea, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **114**:78-112, 1928.

21. Herz, E.: Die amyostatischen Unruheerscheinungen: Klinisch-kinematographische Analyse ihrer Kennzeichen und Begleiterscheinungen, *J. f. Psychol. u. Neurol.* **43**:3-182, 1931.

22. Balthasar, K.: Ueber das Syndrom des Corpus Luys an Hand eines anatomisch untersuchten Falles von Hemiballismus, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **128**:702-720, 1930.

23. Davison, C., and Goodhart, S. P.: Monochorea and Somatotopic Localization, *Arch. Neurol. & Psychiat.* **43**:792-803 (April) 1940.

24. Moersch, F. P., and Kernohan, J. W.: Hemiballismus: A Clinicopathologic Study, *Arch. Neurol. & Psychiat.* **41**:365-372 (Feb.) 1939.

25. Bucy, P. C.: The Neural Mechanisms of Athetosis and Tremor, *J. Neuro-path. & Exper. Neurol.* **1**:224-239, 1942.

26. Keschner, M.: Dyskinesias, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 10, p. 307.

the pattern of ballistic movement has not the slightest resemblance to that of choreiform movements, yet many physicians designate these cases as hemichorea." In recent years a converse tendency has become apparent (noted also by Bertrand and Christophe,²⁷) by which a variety of hemilateral involuntary movements are reported as "hemiballism," without support of a full description of symptoms or of autopsy.

An indication of the semantic character of the problem arose during a meeting of German neurologists, at which Hallervorden²⁸ presented a motion picture record of a case of "lively hyperkinesia," with a diagnosis of hemiballism, but "the anticipated hemorrhage into the corpus Luysi did not appear" and only senile changes of the striatum, thalamus and subthalamic nuclei were to be seen. In the ensuing discussion, Bonhoeffer would not agree that the movements described were those of ballism and stated that he preferred to designate them as those of senile chorea only.

Thus, it appears that there has been a general, but not unanimous, acknowledgment that a violent hemichorea, appropriately termed hemi-

TABLE 2.—*Terminology Employed for Clinical Phenomena Accompanying Localized Lesions of Subthalamic Nucleus*

Term used.....			Ballism	Chorea	Other Terms
No. of cases.....			20	8	2
Language of report.....	German	English	French	Italian	Spanish
No. of cases.....	16	6	5	2	1

ballism, succeeds lesions localized in the contralateral subthalamic nucleus. There is disagreement whether the symptom is specific for, and limited to, such lesions. To determine whether hemiballism as a symptom is an entity and to ascertain what relation, if any, the subthalamic nucleus bears to the symptom was the purpose of this review of the clinical and clinicopathologic literature.

Method of Study.—Ballism was considered a pattern of dyskinesia characterized by continuous, violent, coordinated involuntary activity involving the axial and proximal appendicular musculature such that the limbs were flung about. Search was made in the literature for mention of this symptom, regardless of terminology (table 2), and for the pathologic changes with which it was associated. Descriptions of pathologic changes in the subthalamic nuclei were also sought, whether or not they were accompanied with symptoms and signs.

27. Bertrand, I., and Christophe, J.: Étude anatomo-clinique d'un cas d'hémi-ballisme: Hémorragie linéaire du corps de Luys avec extension au locus niger, *Rev. neurol.* 74:140-141, 1942.

28. Hallervorden: Pathologisch-anatomische Demonstrationen; Hemiballismus, *Zentralbl. f. d. ges. Neurol. u. Psychiat.* 73:724, 1934.

From these two approaches a series of approximately 60 case reports was obtained. Reports in which descriptions of movements and pathologic changes were considered sufficiently complete and accurate were analyzed. Thirty of these cases (part II) proved to be instances of hemiballism associated with pathologic changes localized in the subthalamic nucleus. The circumstances present in the 30 remaining cases are discussed in a separate section (part III), which includes reports of 10 cases of hemiballism and lesions of the subthalamic nucleus without sufficient clinical or pathologic description to merit inclusion in part II.

II. HEMIBALLISM WITH LOCALIZED LESIONS OF SUBTHALAMIC NUCLEUS

Clinical Manifestations.—The clinical pictures in the 30 cases collected by the method outlined in the preceding section were so similar that they may be presented in composite form.

The average age of the patients was 64, with an age distribution unusual for its approximation to the "normal," or bell-shaped, curve (table 3). Seventeen patients were females and 13 males. The clinical finding of arteriosclerosis and hypertension was common, and the latter was frequently present to a formidable degree, but rather good health prior to onset of the symptom was notable.

TABLE 3.—*Age Distribution of Patients with Hemiballism and Localized Lesions of the Subthalamic Nucleus*

Age group, yr.....	40-49	50-59	60-69	70-79	80-89	Not Stated
No. of cases.....	1	8	10	8	2	1

As a rule the onset and development of the symptom were sudden (over a period of hours) and could be correlated largely with the nature of the pathologic change (table 8); but in Wulff's case,²⁹ with a slow-growing tubercle in the subthalamic nucleus, the movements also appeared suddenly.

The involuntary activity that soon reached such dramatic expression began at times with little more than twitchings at the angle of the mouth or with the flinging of an article from the hand. Although in many of the cases of hemorrhage the movement was imposed on a previously hemiplegic side (always coincident with return of a degree of voluntary control), transient aphasia or a period of malaise was frequently the only preliminary indication of the violent symptom later to appear.

The involuntary movements were usually confined to the side opposite the lesion (hemiballism), although less typical ballistic movements

29. Wulff, H.: Corpus Luysi und das hemiballistische Syndrom, *Acta psychiat. et neurol.* 7:999-1019, 1932.

were observed ipsilaterally in some instances. Monoballism was described by Marcus and Sjögren,³⁰ and, by strict definition, the cases of Greiff³¹ and Balthasar²² (first case) showed monoballism of an upper extremity, rather than hemiballism. The head was sometimes jerked about on the neck. Speech and swallowing were now and then impaired, and at times even extrusion of the tongue was forceful and continuous. The face participated by violent grimacing in several cases, and the relation of its involvement to the topographic distribution of destruction within the nucleus suggested to some authors a degree of somatotopy (see page 685).

Such movements are not uncommon with many of the choreas, however, and it was in the extremities that the most remarkable and distinctive movements appeared. Flings and hurlings of the upper extremities and kickings and poundings of the lower extremities, of the greatest abruptness and violence, persisted through every waking moment. Their force and amplitude derived from the coordinating activity of the muscles about the proximal joints and of the related axial musculature. The muscles of the trunk would sometimes contribute further to the pattern by twisting the torso and hips. Hypotonia of the affected muscles, noted as present in 9 cases, and present by inference from the description in 4 other cases, appeared to contribute to the amplitude and freedom of the activity. Abrasions and lacerations from the flailings were commonly reported complications.

Although movements might repeat themselves, no regular rhythm was followed. Sometimes appearing almost "voluntary" in their coordination, the patterns of flexion and extension, abduction, adduction and rotation changed constantly without particular sequence, and could be interrupted by the patient only momentarily, if at all, and with great effort. They appeared almost instantly on waking, usually grew worse during the day, were uniformly and almost characteristically exacerbated by attention or emotion, tended to appear in increased violence after external restraint and were constantly present except during sleep, when they ceased altogether, as in any form of chorea.

Chloral hydrate, paraldehyde, scopolamine, morphine, stramonium, curare and atropine were given therapeutic trial in various cases. The sedatives decreased the violence of the movements and sometimes permitted sleep, which might otherwise have been unobtainable. Although autopsy was not performed in their cases, Schob³² described

30. Marcus, H., and Sjögren, H.: L'hémiballisme et le corps de Luys, *Rev. neurol.* **70**:1-28, 1938.

31. Greiff, F.: Zur Localization der Hemichorea, *Arch. f. Psychiat.* **14**:598-624, 1883.

32. Schob, F.: Hemichorea und Hemiathetose nach Schädeltrauma, *Deutsche Ztschr. f. Nervenhe.* **65**:210-218, 1920.

an instance of hemiballism following fracture of the skull which was relieved by subsequent excision of a cyst, and Jermutowicz³³ and Kulenkampff³⁴ reported surgical efforts to ameliorate the symptom.

Patients seized with such extensive involuntary activity were distraught and exhausted; they attempted to quiet their afflicted extremities with their normal ones, lay on them or restricted them with bedclothes. Bertrand and Garcin³⁵ reported a case in which lashing of the arm to the body was resorted to by the patient's husband. In Marcus and Sjögren's³⁰ second case the patient committed suicide by drowning on discharge from the hospital, almost two years after onset of the movements.

Symptoms of confusion, disorientation or dementia, which some authors (e. g., Martin¹⁹ and Bertrand and Christophe²⁷) sought to include in the syndrome of damage to the nucleus, were by no means

TABLE 4.—*Incidence of Mental Symptoms with Lesions of the Subthalamic Nucleus*

A. Cases of hemiballism with lesions of nucleus and lesions elsewhere (30)	
Mental symptoms noted to be absent.....	6
Mental symptoms present.....	14
Of these, present only terminally.....	3
Mental symptoms not noted.....	10
Total.....	30
B. Cases in section A with localized lesions of nucleus only (13)	
Mental symptoms noted to be absent.....	4
Mental symptoms present.....	6
Of these, present only terminally.....	2
Mental symptoms not noted.....	3
Total.....	13

invariably associated with such a pathologic change (table 4). Only 4 of the 13 patients with localized lesions alone showed mental symptoms other than those which appeared during the terminal stage of the illness. Sensory or reflex changes were absent unless there were lesions elsewhere in the brain.

Death occurred within several days to several months of the onset. Hemiballism persisted unabated until death, for as long as twelve (Touche¹³), or even nineteen (von Sántha³), months. Although in

33. Jermutowicz, W.: Un cas d'hémi-ballismus partiellement amélioré après intervention périphérique, *Rev. neurol.* **55**:374-375, 1931.

34. Kulenkampff, D.: Ueber die sogenannte Hemichorea posthemiplegica (Hemi-ballismus) und die Bedeutung der Pyramidenbahnen, *Zentralbl. f. Chir.* **65**:2466-2470, 1938.

35. Bertrand, I., and Garcin, R.: Étude anatomo-clinique d'un cas d'hémi-ballismus: Lésion dégénérative du corps de Luys et de la zona incerta, *Rev. neurol.* **2**: 820-828, 1933.

at least 2 cases (Marcus and Sjögren,³⁰ cases 4 and 5 [without autopsy]) the condition showed remission, the prognosis for recovery was grave. Patients rarely lived with the symptom more than four or five weeks; and the commonest cause of death was pneumonia (table 5). During the terminal coma the movements frequently diminished, or ceased entirely.

Pathologic Changes in the Subthalamic Nucleus.—Destruction of the subthalamic nucleus, without noteworthy coexisting or antecedent pathologic change elsewhere, was described in 13 of these 30 cases of hemiballism.

Owing to the numerous and intimate relations of the nucleus, one or more of the adjacent structures were not uncommonly involved. These structures included the overlying dorsal divisions of the ansa lenticularis and thalamic fasciculi; the zona incerta, lying between them; the internal capsule, lateral to the nucleus; the substantia nigra, ventrally, and the fusion of the dorsal and ventral divisions of the ansa lenticularis, medially (table 6). But in all these cases the lesion

TABLE 5.—*Causes of Death in Cases of Hemiballism*

Cause of death.....	Pneu- monia	Cardiac Failure	"Ex- haus- tion"	Cerebro- vascular Disease	Pyelitis	Suicide	No Infor- mation	Total
No. of cases.....	13	3	3	1	1	1	8	30

of the nucleus was common, and in the cases of Fischer¹⁶ and Pelnář and Siki³⁶ it was limited strictly to the nucleus, a remarkable confinement in a structure roughly the shape and dimensions of a small lima bean.

Destruction localized to the subthalamic nucleus, but having coexisting or antecedent pathologic changes elsewhere, occurred in 17 of the 30 cases (table 7). In addition to hemiballism, symptoms referable to other regions of the brain were present; but in none of the cases was the significance of the localized damage to the nucleus really in question. In evaluation of the pathologic changes, the estimated pathologic age of the lesion in relation to the duration of the hemiballism was frequently helpful, since the observation of an old softening in the cerebellum and a recent hemorrhage in the subthalamic nucleus left little doubt as to which was related to a symptom of eight days' duration. The presence of gross cerebral arteriosclerosis, reported in the majority of cases, might have been anticipated from the advanced age of the patient group.

36. Pelnář, J., and Siki, H.: L'hémiballisme, le ballisme aigu et le corps de Luys, *Rev. neurol.* 2:328-331, 1929.

Despite the sequence of published cases and the increasing concentration of attention on the region, no case appeared in which an asymptomatic localized lesion of the nucleus was present.

As was pointed out by Martin,² it is possible that certain structures must remain intact for hemiballism to appear on destruction of the nucleus. In Kelman's³⁷ first case the movements ceased during hospitalization, with a dramatic worsening of the patient's status; and autopsy revealed that practically the entire hemicerebrum contralateral to the ballistic movements had been destroyed by a hemorrhage which

TABLE 6.—*Localized Pathologic Change in the Subthalamic Nucleus Without Lesions in Distant Parts of the Cerebrum*

Lesion	Author	Date	Adjacent Area Affected
Hemorrhage	von Economo ¹⁵	1910	Substantia nigra, tegmentum, thalamus
Hemorrhage	Fischer ¹⁶	1911	None
Hemorrhage	Oampora ⁴³	1922	Substantia nigra, capsule of red nucleus, Forci's field
Hemorrhage	Martin ²	1927	Internal capsule, lenticular fasciculus (H ₂)
Hemorrhage	Jakob, C.: Arch. argent. de Neurol. 2: 1-15, 1928	1928	Substantia nigra, rubrolenticular fasciculus, zona incerta
Hemorrhage	Pelnář and Siki ³⁰	1929	None
Hemorrhage	Martin ^{19b}	1934	Lenticular fasciculus, zona incerta
Préciriblé	Bertrand and Garcin ³⁵	1933	Capsule of red nucleus, zona incerta
Préciriblé	Drouet, P, L., Michon, P., and others: Bull. et mém. Soc. méd. d. hôp. de Paris 54: 1085-1089, 1938	1938	Zona incerta
Hemorrhagic softening	Canfield, R. M., and Putnam, J. J.: Bost. M. & S. J. 111: 220-223, 1884	1884	Internal capsule, substantia nigra, tegmentum
Metastatic carcinoma	Bonhoeffer, K.: Monatschr. f. Psychiat. u. Neurol. 77: 127-143, 1930	1930	Substantia nigra, thalamic fasciculus (H ₁)
Tubercle.....	Wulff ²⁹	1932	Internal capsule, rubrothalamic fasciculus, lenticular fasciculus
Infarets	Moersch and Kernohan ²⁴	1939	Lenticular and thalamic fasciculi?

was distinct from a hemorrhage into the subthalamic nucleus of the same side, and apparently had occurred subsequent to it. Again, in Segall's case³⁸ of hemorrhage into the subthalamic region, extensive involvement of the midbrain, including almost the whole internal capsule, and ventricular hemorrhage were present, and hemiballism failed to appear. Balthasar²² commented on a case of hemorrhage involving the subthalamic nucleus, without involuntary movements, in which the

37. Kelman, H.: Hemiballismus: Clinicopathologic Study of Two Cases, J. Nerv. & Ment. Dis. 101:363-371, 1945.

38. Segall, E.: Ein Beitrag zur Pathologie des Corpus Luysi, Monatschr. f. Psychiat. u. Neurol. 52:156-161, 1922.

TABLE 7.—*Localized Lesions of the Subthalamic Nucleus Complicated by Lesions Elsewhere, and Associated Ballism*

Case	Date	Adjacent Areas Affected	Site of Other Lesions
Hemorrhage into Subthalamic Nucleus			
Greiff ³¹	1883	Internal capsule	Ipsilateral thalamus and occipital lobe; contralateral cerebellar hemisphere
Juha and Rakonitz ⁴⁸	1937	Lenticular fasciculus	Ipsilateral pallidum and anterior nucleus of thalamus; contralateral substantia nigra
Kelman ³⁷ (first case).....	1945	None ?	Hemisphere, thalamus and basal ganglia (subsequent to subthalamic lesion)
Matzdorff ⁴	1927	Thalamic and lenticular fasciculi; ansa lenticularis	Ipsilateral striatum and thalamus
von Sántha ³	1928	Zone incerta; lenticular fasciculus	Contralateral cortex; basal ganglia and thalamus
Oiberall, H., and Samet-Amhrus, V.: Ztschr. f. d. ges. Neurol. u. Psychiat. 131 : 502-513, 1913	1913	Substantia nigra; thalamic fasciculus	Ipsilateral pallidum and putamen
Wenderowicz ²⁰	1928	Internal capsule; lenticular fasciculus	Ipsilateral occipital lobe
von Sántha ⁴⁷	1932	Lenticular fasciculus	Contralateral lateral thalamus and medial geniculate body
A. Jakob ¹ (case 19).....	1923	Rubrothalamic fasciculus; thalamic and lenticular fasciculi	Bilateral status cribrosus of striopallidum
Touche ¹³	1901	Internal capsule; red nucleus; substantia nigra	Ipsilateral lateral nucleus of thalamus; retrolenticular internal capsule
Marcus and Sjögren ³⁰ (case 1)	1938	Region of subthalamic nucleus	Pons
Gregory, H. S.: New York State J. Med. 38 : 635-636, 1938	1938	Tegmentum	Basal ganglia (scattered softenings)
Syphilitic Necrosis of Subthalamic Nucleus			
Bodechtel, G., and Higl, W.: Arch. f. Psychiat. 102 : 654-669, 1934	1934	Red nucleus (anterior part)	Contralateral pallidum; ipsilateral juxtathalamic area; ansa lenticularis and lenticular fasciculus (H ₂)
Kutch, T.: Ztschr. f. d. ges. Neurol. u. Psychiat. 164 : 404-416, 1939	1939	Internal capsule; lenticular fasciculus	Meninges; contralateral caudate nucleus; putamen and internal capsule
Softenings of Subthalamic Nucleus			
Balthasar ²²	1930	None ?	Contralateral cortex; striopallidum and thalamus
Marcus and Sjögren ³⁰ (case 2)	1938	Internal capsule	Ipsilateral thalamus
Neoplasm Metastatic to Subthalamic Nucleus			
Bremme ⁴²	1919	Internal capsule; substantia nigra; lenticular fasciculus	Contralateral cerebellum and cerebellar peduncle

dorsal thalamus, the striatum and much medullary substance were also destroyed. It is of interest that the movements of hemiballism in Touche's case¹³ ceased temporarily during two intercurrent attacks of bronchopneumonia.

Symptoms Referable to the Autonomic Nervous System.—Few writings on hemiballism have failed to include comment on the association of symptoms of disturbance of the autonomic nervous system with lesions of the subthalamic nucleus. An autonomic function was suggested by the experiments of Karplus and Kreidl,³⁹ whose stimulation of the region in animals produced a galaxy of symptoms referable to activity of the sympathetic nervous system. Speculations by Schrottenbach⁴⁰ and Gerstmann⁴¹ on their clinical experience served to fortify the concept. Of the 30 cases which form the basis of this review, symptoms of autonomic disturbance which might be related to the pathologic changes in the subthalamus were present in only 5.

TABLE 8.—*Type of Lesion and Mode of Onset*

No. of Cases	Type of Lesion	Mode of Onset *	
		Sudden	Gradual
19	Hemorrhage.....	15	1
3	Softening.....	2	1
2	Metastasis.....	0	2
2	Syphilitic necrosis.....	0	2
1	Tubercle.....	1	0
1	Infarct.....	1	0
2	Degeneration.....	1	1
30		20	7

* Information lacking in 3 cases.

In Bremme's⁴² case there were hyperhidrosis over the left side, especially of the face, and vasodilatation on the same side of the face. A metastatic lesion involved the subthalamic nucleus, internal capsule, substantia nigra and lenticular fasciculus on the left side, and the ballistic movements were contralateral. In Martin's case,² moderate hemihyperhidrosis was present on the side of the ballistic movements, and a hemorrhage involved the contralateral subthalamic nucleus, inter-

39. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halssympathicus, Arch. f. d. ges. Physiol. **129**:138-144, 1909.

40. Schrottenbach, H.: Beiträge zur Kenntnis der Uebertragung vasovegetativer Funktionen im Zwischenhirn, Ztschr. f.d.ges.Neurol. u. Psychiat. **23**:431-510, 1914.

41. Gerstmann, J.: Zur Frage der sympathischen Gehirnbahnen, Jahrb. f. Psychiat. u. Neurol. **34**:287-321, 1913.

42. Bremme, H.: Ein Beitrag zur Bindarmchorea, Monatschr. f. Psychiat. u. Neurol. **45**:107-120, 1919.

nal capsule and lenticular fasciculus. In Greiff's³¹ case there were hyperthermia and vasodilatation of the arm on the side of the ballistic movements and a hemorrhage involving the contralateral subthalamic nucleus and internal capsule; hemorrhages also existed in the occipital lobe on the side of the lesion and in the medullary core of the cerebellar hemisphere on the side of the symptom. Pallidohypothalamic fibers known to run in the ansa lenticularis were interrupted in the first 2 cases and may have been implicated in the third. Why the autonomic symptoms were ipsilateral to the lesion in Bremme's case and contralateral in the other 2 cases is not clear. Somnolence, possibly a symptom of "vegetative function," was present in the cases of Matzdorff⁴ and Wenderowic,²⁰ but its significance in patients 80 and 81 years of age, respectively, is questionable. Edema of the affected hand and forearm was noted clinically in Bertrand and Garcin's⁸⁵ case and at autopsy in Campora's⁴³ case, being associated in the latter with lividity

TABLE 9.—*Somatotopical Relations of the Subthalamic Nucleus in Cases of Hemiballism*

	No. of Cases
Favoring somatotopic relations	
Face affected and oral pole destroyed.....	17
Face free and oral pole intact.....	2
Not favoring somatotopic relations	
Face involved and oral pole intact.....	1
Face free and oral pole involved.....	1
Information lacking	9
Total.....	30

of the affected side. Reference may be made to Friedman's⁴⁴ reports of hemiedema associated with hemiplegia, but whether these signs were secondary to an autonomic change or whether they were due to the abnormal muscular activity of hemiballism is difficult to decide.

In the remaining 25 cases no mention was made of symptoms of autonomic disturbance. The equivocal nature of the 5 cases noted here renders it doubtful whether the subthalamic nucleus possesses any autonomic function.⁴⁵

43. Campora, G.: Sopra un caso di emicorea con reperto necroscopio, *Pathologica* 14:41-43, 1922.

44. Friedman, A. P.: Hemiedema in Hemiplegia: Report of Three Cases, *Bull. Los Angeles Neurol. Soc.* 7:194-197, 1942.

45. It may be reiterated (Wilson⁵⁸) that deduction of the function of a neural structure from the symptoms following its destruction is not always warranted, an objection which applies to analysis of kinetic, as well as autonomic, activities of the subthalamic nucleus by this method.

Somatotopic Relations.—The Vogts ⁴⁶ (page 774) expressed the belief that a definite topical relation exists between the parts of the striopallidum and the subthalamic nucleus. Von Sántha ⁴⁷ concluded that the head, arms, trunk and legs were represented by different parts of the nucleus, proceeding in an orocaudal direction, because the face was affected and the entire nucleus destroyed in his first case,³ while no involuntary facial movements appeared in his second case,⁴⁷ in which the oral pole was spared. Martin ^{19b} and Juba and Rakonitz ⁴⁸ submitted their cases of hemiballism as evidence of a somatotopic arrangement in the subthalamic nucleus. Table 9 suggests, in agreement with these authors, that involuntary facial movements usually occur with involvement of the oral pole of the structure.

TABLE 10.—*Association of Involuntary Movement with Nonfocal Lesions in the Subthalamic Nucleus*

Author	Date	Movement	Pathologic Change
O. and O. Vogt ⁴⁶ (cases 20, 21, 22)	1920	Spasms; athetoses	Degenerations of striatum and pallidum; alteration of subthalamic nucleus (decrease in size, poverty of capsule)
A. Jakob ¹ (case 7)....	1923	Generalized gross choreiform movements	Senile changes in many regions, including subthalamic nuclei
Weil ⁵⁶	1928	Choreiform movements of right arm and shoulder	Atrophy of striatum and pallidum; gliosis and pigmentation of neurons in subthalamic nuclei
Schroeder, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. 23 : 431-510, 1914	1931	Choreiform jerklings of fingers, toes and shoulders	Huntington's disease; atrophy of subthalamic nuclei, gliosis and neuronal degeneration

In Balthasar's ²² first case the oral pole was chiefly destroyed, and here the face and the upper extremity were more severely affected than the lower extremity. Similarly, however, less severe involvement of the lower extremities was noted in most cases of the present series.

III. BALLISM WITH LESIONS ELSEWHERE

Ballism was described also (*a*) in 6 cases in which pathologic changes spared the subthalamic nucleus but interrupted what are presumed to be its connections, (*b*) in at least 2 cases in which pathologic

46. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen der striären Systems, J. f. Psychol. u. Neurol. **25**:627-846, 1920.

47. von Sántha, K.: Hemiballismus und Corpus Luysi: Anatomische und pathophysiologische Beiträge zur Frage des Hemiballismus nebst Versuch einer somatotopischen Lokalisation im Corpus Luysi, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:321-342, 1932.

48. Juba, A., and Rakonitz, E.: Ueber einen Fall von Hemiballismus (Beitrag zur Somatotopie des Corpus Luysi), Arch. f. Psychiat. **106**:629-642, 1937.

changes in the nucleus were part of a more generalized process and (c) in at least 4 cases in which no demonstrable change of the nucleus or connections was discerned. These reports will now be presented.

Pathologic Changes Interrupting Connections of the Subthalamic Nucleus.—Papez, Bennett and Cash⁴⁹ reported a case of hemiballism with lesions in the ipsilateral pallidum and the contralateral prerubral field, the subthalamic nuclei being intact. Although the fiber connections of the nucleus are not completely understood, at least some of its afferent fibers arise in the external segment of the pallidum, and some efferent fibers cross to the prerubral field in the subthalamic decussation. Their interruption is presumed to have caused the symptom in this case. In Kelman's³⁷ second case, although the tip of the oral pole of the nucleus was involved, the carcinomatous metastasis "was so placed as to affect essentially the subthalamicotegmental fibers," which constitute an ipsilateral efferent connection. Lewandowsky and Stadelmann⁵⁰ reported a case of a condition not clearly hemiballism by description, but with hemorrhagic softening of the retrolenticular portion of the internal capsule, extending somewhat into Forel's field. This lesion may have interrupted afferent fibers to the nucleus from the pallidum, which pierce the internal capsule in the region.

Balthasar⁵¹ was inclined to attribute the ballism in his case to softening in the external segment of the contralateral pallidum and interruption of the subthalamic afferent fibers, although pathologic changes were present in both nuclei, being more extensive contralateral to the ballistic movements. Alexander⁵² expressed the opinion that the latter changes deserved severer indictment, and placed the case with those of nonlocalized pathologic processes in which the nuclei take part. The metastasis in Bonhoeffer's case¹² and the tubercle in Bianchi's⁵³ were situated in the pons and involved the medial lemniscus; they may have been related to the hemichorea present though interruption of the descending subthalamicotegmental fibers as they pass caudad medial to this tract. The diagnosis of ballism may be inferred from

49. Papez, J. W.; Bennett, A. E., and Cash, P. T.: Hemichorea (Hemiballismus): Association with a Pallidal Lesion, Involving Afferent and Efferent Connections of the Subthalamic Nucleus; Curare Therapy, *Arch. Neurol. & Psychiat.* **47**:667-676 (April) 1942.

50. Lewandowsky, M., and Stadelmann, E.: Chorea apoplectica, *Ztschr. f.d.ges. Neurol. u. Psychiat.* **12**:530-539, 1912.

51. Balthasar, K.: Ueber die Beteiligung des Globus pallidus bei Athetose und Paraballismus, *Deutsche Ztschr. f. Nervenhe.* **148**:243-261, 1939.

52. Alexander, L.: The Fundamental Types of Histopathologic Changes Encountered in Cases of Athetosis and Paralysis Agitans, *A. Research Nerv. & Ment. Dis. Proc.* **21**:389, 1942.

53. Bianchi, L.: Contributo alla conoscenza della emicorea sintomatica, *Ann. di nevrol.* **27**:1-42, 1909.

the description in Bonhoeffer's case, although in both cases the condition was reported as hemichorea.'

These 6 cases constitute a suggestive, but not conclusive, body of evidence that hemiballism may be produced by lesions interrupting the connections of the subthalamic nucleus.

Nonlocalized Pathologic Changes in the Subthalamic Nucleus.—Ballism was reported in Balthasar's ⁵¹ case, already referred to, in which pathologic changes in the subthalamic nuclei were part of a diffuse process. His case, in which left hemiballism and, finally, paraballism were present, was characterized by widespread senile changes with softening of the external segment of the right pallidum and atrophy and senile alterations in the subthalamic nuclei, more particularly on the right. The Vogts ⁵⁴ described what might be termed "holoballism," with *état fibreux* of the putamen and caudate nucleus and atrophy of the pallidum and subthalamic nucleus bilaterally. In Myslivecek's case, cited by Pelnář and Sikl,⁵⁵ there was bilateral chorea, which, according to the latter, was ballistic. Instead of the anticipated bilateral subthalamic hemorrhage, autopsy revealed cerebral atrophy and diffuse degeneration of neurons in the striatum, thalamus and subthalamic nuclei.

With these reports also belongs the case of Titica and Bogaert,^{55a} characterized by monoballistic movements of the right upper extremity, the pathologic changes being diffuse and including extreme atrophy of the right subthalamic nucleus.

That such nonlocalized pathologic change in the subthalamic nucleus does not consistently evoke ballism was evidenced by the 6 cases in table 10, in which were presented a variety of involuntary movements, but not ballism. In the cases reported by Weil ⁵⁶ and A. Jakob, ballism may have existed, but its presence could not be inferred from the clinical descriptions.

Hemiballism Without Pathologic Changes in the Subthalamic Nuclei or Their Connections.—In the clinicopathologic reports of the following cases, the clinical description of ballism can scarcely be in doubt, and the subthalamic nuclei and their connections were devoid of pathologic changes. Fragnito and Scarpini ⁵⁷ reported such a case. After slight left hemiplegia and transient "psychomotor agitation," a laborer aged

54. Vogt and Vogt,⁴⁶ p. 709.

55. Pelnář and Sikl,⁸⁶ p. 331.

55a. Titica, J., and van Bogaert, L.: Heredo-Degenerative Hemiballismus; a Contribution to the Question of Primary Atrophy of the Corpus Luysi, *Brain* **69**:251-263, 1946.

56. Weil, A.: A Contribution to the Pathology of Hemichorea, *Brain* **51**:36-45, 1928.

57. Fragnito, O., and Scarpini, V.: *Reperto anatomopatologico in un caso di emicorea sintomatica*, *Riv. di pat. nerv.* **31**:524-531, 1926.

80 exhibited "choreic excitation" of the upper and lower extremities on the left side, with particular involvement of the deltoid muscle and "expansive" movements, which persisted more than three years. At a carefully reported autopsy, lacunar softenings of the head of the caudate nucleus and the internal portion of the putamen, as well as an insignificant, pea-sized softening in the medial nucleus of the optic thalamus, were observed contralaterally. In answer to Martin's question,^{19b} Fragnito specifically denied the presence of pathologic changes in the corpus Luysi, Forel's field and the medial lemniscus.

In Wilson's ⁵⁸ case there developed typical right hemiballism,⁵⁹ which persisted and progressed for eleven years, until it was necessary to fashion an iron frame to protect the patient, an old woman, from the blows of her own arm. Autopsy revealed atrophy of the left postcentral gyrus as the sole lesion. Careful histologic study failed to disclose any pathologic changes in the basal ganglia, and Wilson's statement on the condition of the subthalamic nucleus was pointed and emphatic: ". . . no alterations of any kind among the cells or fibers; they were normal."

Austregesilo and Borges Fortes ⁶⁰ reported the case of a woman aged 32 who showed ballistic movements of the left side after three attacks of apoplexy—"movements of the limbs, which were rapid, violent, spasmodic and disorderly, being principally hyperextensions (hemiballism)." Cortical softening was observed in the island of Reil, but no pathologic changes were discovered in the subthalamic region.

Rothfield and Demianowska ⁶¹ reported a case of hemiballism in which the subthalamic nuclei were intact. Lesions were described, however, in the contralateral internal capsule and neostriatum, and it is conceivable that the former may have interrupted fibers to the nucleus.

Dunlap ⁶² described involuntary movements of the whole body, but especially of the upper extremity—"coarse, awkward, and of wide excur-

58. Wilson, S. A. K.: Die Pathogenese der unwillkürlichen Bewegungen mit besonderer Berücksichtigung der Pathologie und Pathogenese der Chorea, Deutsche Ztschr. f. Nervenhe. **108**:4-38, 1929.

59. Wilson's description ⁵⁸ (page 16) is striking: "It [the symptom] consisted of wild choreiform movements of the arm, limited to the right side, and affecting the larger joints much more markedly than the smaller ones. The arm was flung about in all directions, and struck the patient and those who came unknowingly into her vicinity; it was thrown around against pieces of furniture."

60. Austregesilo, A., Jr., and Borges Fortes, A.: Étude anatomo-clinique d'un cas d'aphasie de Wernicke avec hémiballisme, Rev. sud-am. de méd. et de chir. **2**: 1111-1124, 1931.

61. Rothfield, J., and Demianowska, M.: Przyczynek do patogenezy hemibalizmu, Polska gaz. lek. **15**:569-575, 1936 (German summary, p. 574).

62. Dunlap, C. B.: Pathologic Changes in Huntington's Chorea, with Special Reference to the Corpus Striatum, Arch. Neurol. & Psychiat. **18**:867-943 (Dec.) 1927.

sion"; hence, presumably ballistic in a woman aged 63 with Huntington's disease (hereditary chronic progressive chorea) (case 938, page 937); he noted no particular changes in the subthalamic nuclei in this case or in any other cases of the disease which he studied. Both Wenderowic²⁰ and Martin^{19b} asserted they had seen ballistic movements in patients with Huntington's disease. Davison and Goodhart⁶³ described ballistic movements in a case of dystonia musculorum deformans; besides scattered lesions in the cerebrum, they noted that the capsule of the subthalamic nucleus was lightly stained. Finally, Sydenham's chorea is a hemichorea in many cases (almost 50 per cent, according to Wilson⁶⁴); ballistic movements may be observed in many such cases, and no consistent changes in the subthalamic nucleus have been recognized.

Fundamentally dissimilar symptoms may become confused in the process of written description. It is entirely possible that a comparison of motion picture records, were they available, would necessitate a reclassification of these and other cases, and perhaps set hemiballism apart as a symptom unrelated to any pathologic changes other than those of the subthalamic nucleus. But it appears inescapable that in at least 3 cases (Fragnito and Scarpini⁵⁷; Wilson,⁵⁸ and Austregesilo and Borges Fortes⁶⁰) hemiballism existed without demonstrable pathologic change in this structure.

Miscellaneous Clinicopathologic Cases.—A number of cases might be included with the 30 cases with localized lesions were it not for inadequacies in the clinical description or pathologic report. Pette⁶⁵ reported a case in which a pea-sized neoplastic metastasis appeared in the "regio subthalamica," and Spatz,⁶⁶ a case in which a fresh hemorrhage destroyed the subthalamic nucleus and involved the internal capsule. The lesion in Pette's case was associated with what was probably hemiballism ("a severe choreiform disturbance of the whole left side of the body"), and that in Spatz's case, with hemiballism by name only. Schaffer⁶⁷ reported a case as one of hemiballism ("violent massive movements") with hemorrhage limited to the contralateral subthalamic nucleus. Kulenkampff³⁴ recorded a case of monoballism of the right upper extremity of three years' duration, in which autopsy showed scarring and atrophy of cells in the lenticular nucleus and, "even macro-

63. Davison, C., and Goodhart, S. P.: Dystonia Musculorum Deformans: A Clinicopathologic Study, *Arch. Neurol. & Psychiat.* **29**:1108-1124 (May) 1933.

64. Wilson,¹⁷ p. 617.

65. Pette, H.: Zur Localization hemichoreatischer Bewegungsstörungen, *Zentralbl. f. d. ges. Neurol. u. Psychiat.* **30**:407-408, 1922.

66. Spatz, H.: Anatomische Abteilung, *Arch. f. Psychiat.* **80**:279, 1927.

67. Schaffer, K.: Ueber Hemiballismus, klinisch und anatomisch, *Zentralbl. f. d. ges. Neurol. u. Psychiat.* **49**:847, 1928.

scopically, an atrophy of the basal nuclei in the region of the internal capsule." In Bertrand and Christophe's²⁷ case, reported as one of hemiballism, a hemorrhage involving essentially the contralateral subthalamic nucleus extended also into the substantia nigra and the capsule of the red nucleus. The evaluation of this case is difficult because of the meager pathologic report and the rather major psychic symptoms.

There are at least 5 cases which may not be classified without further reservations. A case of Souquès and Bertrand,⁶⁸ reported as one of hemichorea, was characterized by choreoathetotic movements of the left side, which dislocated the shoulder by their violence. They had persisted for fifty years, having their onset with post-typhoid hemiplegia at the age of 4 years. Softenings of the contralateral caudate nucleus, putamen and external segment of the pallidum were observed, with extreme atrophy of the subthalamic nucleus on that side. The case may belong with those having interruption of the connections of the nucleus. In Nikitin's⁶⁹ case, postapoplectic hemiballism involving the right side of a patient aged 77 was associated with hemorrhage in the left thalamus, which, as von Sántha stated, "approached within 2 mm. of the dorsal border of the intact subthalamic nucleus." In Hampel's⁷⁰ case, reported as one of hemiballism with a syphilitic basis, gliosis and neuronal degeneration were observed in the putamen and the subthalamic nucleus, being more extensive in the latter contralateral to the ballistic movements, but major psychic symptoms suggested a cautious evaluation. In case 3 of Marcus and Sjögren,⁷¹ that of a woman aged 88 who died of bronchopneumonia twelve months after onset of hemiballism involving the right side, strip-shaped softenings, present bilaterally, involved the thalamus, subthalamic nucleus, internal capsule and a portion of the pallidum contralateral to the ballistic movements, and the same structures on the right except for the subthalamic nucleus.

Whether the involuntary movements shown by Lloyd and Winkelman's⁷² patient were ballistic was not clear from the description; a recent hemorrhage on the opposite side destroyed portions of the striatum and the internal capsule and "impinged on the corpus Luysi."

68. Souques, A., and Bertrand, I.: Sur la fonction motrice du corps strié, à propos d'un cas d'hémichorée suivi d'autopsie, *Rev. neurol.* **33**:988-1002, 1926.

69. Nikitin: Zusammenfassungen internationaler Neurologenkongress zu Bern, 1932; cited by von Sántha⁴⁷ (p. 331).

70. Hampel, E.: Hemiballismus auf luischer Grundlage: Beitrag zur pathologischen Anatomie und Pathogenese des Hemiballismus, *Deutsche Ztschr. f. Nervenhe.* **141**:77-96, 1936.

71. Marcus and Sjögren,³⁰ p. 18.

72. Lloyd, J. H., and Winkelman, N. W.: A Case of Acute Posthemiplegic Choreiform Movements on the Unparalyzed Side: Study of the Basal Ganglia, *Am. J. M. Sc.* **169**:247-253, 1925.

Finally, Kashida's⁷³ case (page 696) combined athetosis, torsion dystonia and hemiballism with a multiplicity of pathologic changes, among which was a diminution in size and absence of capsular fibers of the subthalamic nucleus.

Clinical Cases Without Autopsy.—Some kind of localized change in the subthalamic nucleus seems to have been present with ballism in the clinical cases of Grigoresco and Axente,⁷⁴ Marcus and Sjögren³⁰ (cases 4 and 5) and von Angyal and von Pethe.⁷⁵ The probable pathologic changes were, respectively, hemorrhage, gumma, embolus and syphilitic necrosis. The probable pathologic lesions were more or less obscure in the cases of Jermutowicz,⁸³ Rakonitz,⁷⁶ Alurralde and Sepich,⁷⁷ Urechia and Bumbacescu,⁷⁸ Bauman,⁷⁹ and Teske.⁸⁰

SUMMARY AND CONCLUSIONS

A review of the literature disclosed 30 cases of hemiballism associated with localized pathologic change in the subthalamic nucleus. Analysis of these cases led to the following conclusions:

1. Ballism is a distinct form of involuntary movement characterized by continuous, violent, coordinated activity of the axial and proximal appendicular musculature such that the limbs are flung about.
2. Hemiballism, and sometimes monoballism of the upper extremity, is the apparently inevitable symptom in man of destruction localized in the contralateral subthalamic nucleus (nucleus hypothalamicus; corpus Luysi).
3. There is evidence that interruption of the connections of the subthalamic nucleus may result in hemiballism.

73. Kashida: Ueber Gehirnarteriosclerose des früheren Alters und über die Kombination von corticalen, pyramidalen und extrapyramidalen Symptomen bei der Gehirnarteriosclerose, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **94**:659-702, 1925.

74. Grigoresco, D., and Axente, S.: Syndrom Luysien: Influence du tabac sur les grands mouvements d'hémiballisme, *Rev. neurol.* **1**:361-363, 1931.

75. von Angyal, L., and von Pethe, F.: Ein Fall von Monoballismus luischer Genese, *Arch. f. Psychiat.* **113**:120-125, 1941.

76. Rakonitz, E.: Die Eigenerkrankung des Corpus Luysii; der erste heredo-degenerative Biballismus-Fall, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **144**:225-266, 1933.

77. Alurralde, M., and Sepich, M.: Síndrome de hemibalismo (dos observaciones clínicas), *Prensa méd. argent.* **22**:609-614, 1935.

78. Urechia, C. I., and Bumbacescu, M.: Hémiballisme congénital, *Rev. neurol.* **70**:509-510, 1938.

79. Bauman, C.: Ein Fall von reinem Hemiballismus auf dem Boden eines degenerativen Nervenleidens, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **162**:126-135, 1938.

80. Teske, W.: Beitrag zur Klinik des ballistischen Syndroms, *Nervenarzt* **15**: 424-427, 1942.

4. Hemiballism may appear without demonstrable pathologic change in the subthalamic nucleus or its connections, although such cases are relatively rare.

5. Ballistic movements may appear in a variety of dyskinesias, to which the relation of the subthalamic nucleus is as yet obscure. Their similarity to or identity with those of hemiballism following damage to the subthalamic nucleus awaits a more complete, and preferably cinematographic, comparison.

6. Adequate clinical description and pathologic study will continue to be of value in elucidating the genesis and nature of this remarkable symptom.

630 West One Hundred and Sixty-Eighth Street.

ELECTROENCEPHALOGRAPHIC STUDIES ON INDUCED AND EXCISED EPILEPTOGENIC FOCI IN MONKEYS

BERNARD L. PACELLA, M.D.

LENORE M. KOPELOFF, Ph.D.

AND

NICHOLAS KOPELOFF, Ph.D.

NEW YORK

PREVIOUSLY we¹ reported that the experimental production of epilepsy in the monkey was associated with electroencephalographic abnormality. It was noted that in addition to a primary focus in the region of application of the inciting agent, there was evidence of spread of electroencephalographic abnormality to the opposite side of the brain.²

PRESENT INVESTIGATION

The present study is concerned with more detailed observations regarding the time relation between electroencephalographic evidence of primary and secondary foci and the onset of convulsive seizures. In addition, the effect of ablation of the "active" focus was investigated..

Technic.—In accordance with the method previously described,^{1a} unilateral application of hydrous oxides of aluminum to the motor cortex of 4 monkeys resulted in epileptiform seizures in every instance on physical stimulation. As controls, 3 additional monkeys similarly prepared with noneffective materials at no time manifested convulsive seizures. Electroencephalographic records were taken before operation and at intervals thereafter. A head control apparatus, attached to an animal board and a bandage over the eyes aided in immobilizing the animal. Curare³ was administered intravenously when necessary in doses approximating 1 mg. per kilogram of body weight. This dose of curare was without apparent effect on the electroencephalographic pattern. Electroencephalograms were taken with a two channel Rahm machine, utilizing a bipolar system

From the Departments of Experimental Psychiatry and Bacteriology, New York State Psychiatric Institute and Hospital.

1. (a) Kopeloff, L. M.; Barrera, S. E., and Kopeloff, N.: Recurrent Convulsive Seizures in Animals Produced by Immunologic and Chemical Means, *Am. J. Psychiat.* **98**:881-902, 1942. (b) Pacella, B. L.; Barrera, S. E., and Kopeloff, L. M.: Electroencephalographic Studies on Monkeys with Chronic Jacksonian Seizures, *Federation Proc.* **1**:65, 1942.

2. Pacella, B. L.; Kopeloff, N.; Barrera, S. E., and Kopeloff, L. M.: Experimental Production of Focal Epilepsy, *Arch. Neurol. & Psychiat.* **52**:189-196 (Sept.) 1944.

3. Intocostin, E. R. Squibb & Sons, New York.

TABLE 1.—Electroencephalographic and Clinical Observations on Monkeys with Induced and Excised Epileptogenic Foci

Active Substance *—Alumina Cream †														
Animal 449					Animal 450					Animal 451				
Electroencephalo-gram ‡					Electroencephalo-gram					Electroencephalo-gram				
Left		Right		Seizures †	Left		Right		Seizures	Left		Right		Seizures
Weeks					Weeks					Weeks				
03	±	±	±	0	0	0	0	0	0	0	0	0	0	0
5	++	++	++	0	0	0	0	0	0	0	0	0	0	0
7 1/2	++	++	++	0	0	0	0	0	0	0	0	0	0	0
13	++	++	++	0	0	0	0	0	0	0	0	0	0	0
24	++	++	++	0	0	0	0	0	0	0	0	0	0	0
38	++	++	++	0	0	0	0	0	0	0	0	0	0	0
39	++	++	++	S	S	S	S	S	S	S	S	S	S	S
45	++	++	++	S	S	S	S	S	S	S	S	S	S	S
46	++	++	++	S	S	S	S	S	S	S	S	S	S	S
62	++	++	++	0	0	0	0	0	0	0	0	0	0	0
63	++	++	++	0	0	0	0	0	0	0	0	0	0	0
65	++	++	++	0	0	0	0	0	0	0	0	0	0	0
73	++	++	++	0	0	0	0	0	0	0	0	0	0	0
77	++	++	++	0	0	0	0	0	0	0	0	0	0	0
81	++	++	++	0	0	0	0	0	0	0	0	0	0	0
82	++	++	++	0	0	0	0	0	0	0	0	0	0	0

Control Substances *														
Electroencephalo-gram					Electroencephalo-gram					Electroencephalo-gram				
Left		Right		Seizures †	Left		Right		Seizures	Left		Right		Seizures
Weeks					Weeks					Weeks				
03	±	±	±	0	0	0	0	0	0	0	0	0	0	0
5	++	++	++	0	0	0	0	0	0	0	0	0	0	0
7 1/2	++	++	++	0	0	0	0	0	0	0	0	0	0	0
13	++	++	++	0	0	0	0	0	0	0	0	0	0	0
24	++	++	++	0	0	0	0	0	0	0	0	0	0	0
38	++	++	++	0	0	0	0	0	0	0	0	0	0	0
39	++	++	++	S	S	S	S	S	S	S	S	S	S	S
45	++	++	++	S	S	S	S	S	S	S	S	S	S	S
46	++	++	++	S	S	S	S	S	S	S	S	S	S	S
62	++	++	++	0	0	0	0	0	0	0	0	0	0	0
63	++	++	++	0	0	0	0	0	0	0	0	0	0	0
65	++	++	++	0	0	0	0	0	0	0	0	0	0	0
73	++	++	++	0	0	0	0	0	0	0	0	0	0	0
77	++	++	++	0	0	0	0	0	0	0	0	0	0	0
81	++	++	++	0	0	0	0	0	0	0	0	0	0	0
82	++	++	++	0	0	0	0	0	0	0	0	0	0	0

Rare Earth Oxides														
Animal 453					Animal 454					Animal 430				
Electroencephalo-gram					Electroencephalo-gram					Electroencephalo-gram				
Left		Right		Seizures Opposite	Left		Right		Seizures Opposite	Left		Right		Seizures Opposite
Weeks					Weeks					Weeks				
0	±	±	±	0	0	0	0	0	0	0	0	0	0	0
4	±	±	±	0	0	0	0	0	0	0	0	0	0	0
6	±	±	±	0	0	0	0	0	0	0	0	0	0	0
23	±	±	±	0	0	0	0	0	0	0	0	0	0	0
35	±	±	±	0	0	0	0	0	0	0	0	0	0	0
39	±	±	±	0	0	0	0	0	0	0	0	0	0	0
43	±	±	±	0	0	0	0	0	0	0	0	0	0	0
61	±	±	±	0	0	0	0	0	0	0	0	0	0	0
73	±	±	±	0	0	0	0	0	0	0	0	0	0	0

Zinc Oxide														
Animal 430					Animal 430					Animal 430				
Electroencephalo-gram					Electroencephalo-gram					Electroencephalo-gram				
Left		Right		Seizures Opposite	Left		Right		Seizures Opposite	Left		Right		Seizures Opposite
Weeks					Weeks					Weeks				
0	±	±	±	0	0	0	0	0	0	0	0	0	0	0
71	±	±	±	0	0	0	0	0	0	0	0	0	0	0
72	±	±	±	0	0	0	0	0	0	0	0	0	0	0
72 1/2	±	±	±	0	0	0	0	0	0	0	0	0	0	0
73	±	±	±	0	0	0	0	0	0	0	0	0	0	0
75	±	±	±	0	0	0	0	0	0	0	0	0	0	0
79	±	±	±	0	0	0	0	0	0	0	0	0	0	0
81	±	±	±	0	0	0	0	0	0	0	0	0	0	0
116	±	±	±	0	0	0	0	0	0	0	0	0	0	0
122	±	±	±	0	0	0	0	0	0	0	0	0	0	0

* The agent was applied to the left motor cortex.
† Left and right indicate leads from the left and right side of the cortex. The signs ± to ++ represent increasing degrees of electroencephalographic abnormality, as indicated by the incidence and duration of delta waves, sharp formations and spike potentials.
‡ S indicates seizure; 0, no seizures.
§ Before operation.
|| The electroencephalographic record was unsatisfactory.

of recording. The electrodes consisted of needle clips firmly affixed to the scalp over the prefrontal, motor and occipital regions of both sides of the head. Electroencephalographic abnormalities were classified as slight, moderate and severe, depending on the frequency rate and incidence of slow activity, the irregularity of pattern and the amount of high voltage fast activity.

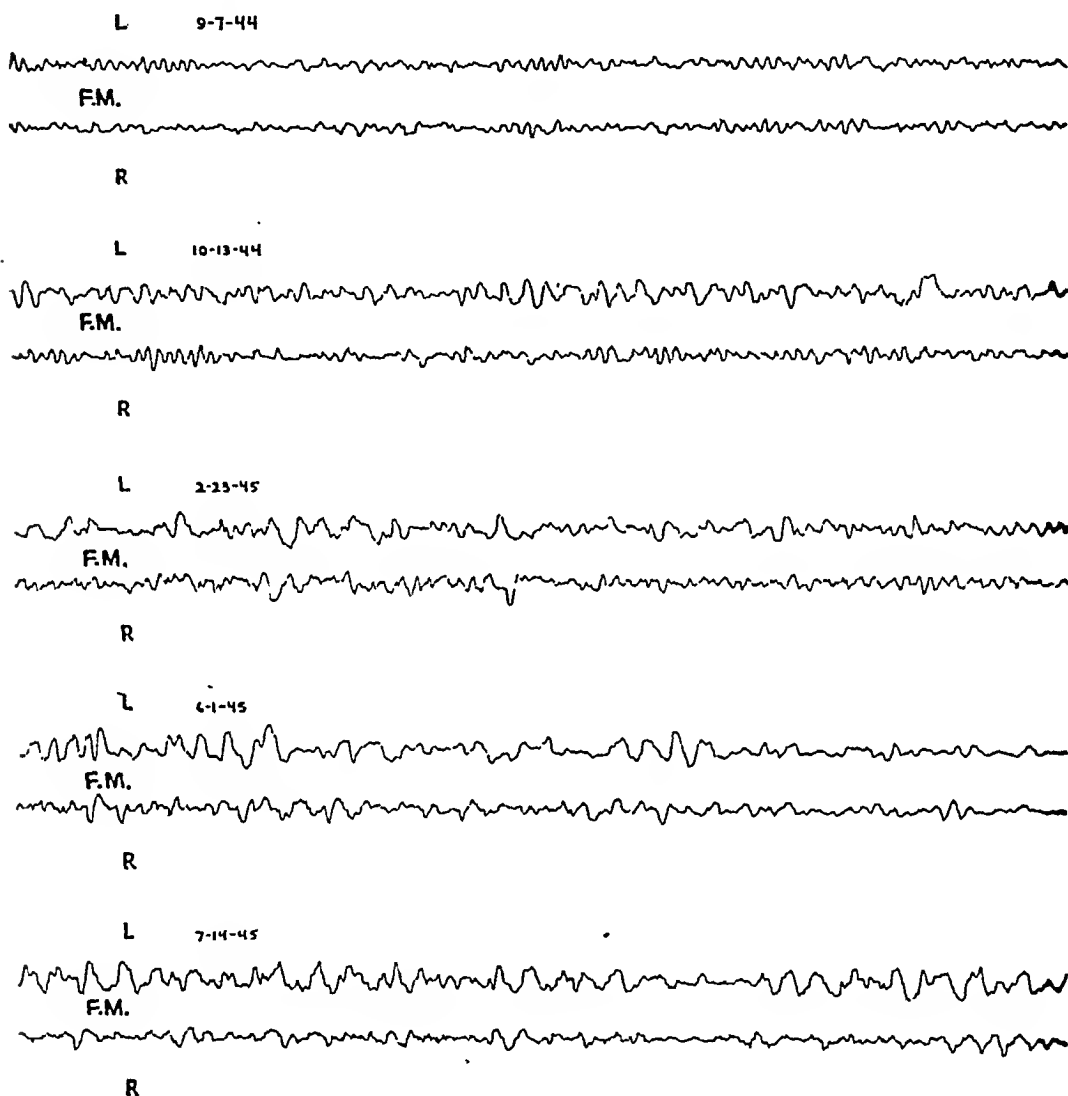


Fig. 1 (monkey 449).—9/7/44: Control tracing prior to operation, taken with bilateral frontomotor leads (*F.M.*) showing normal activity with frequent trains of alpha rhythm.

10/13/44: Five weeks after application of the active agent to the left precentral cortex. No clinical seizures occurred. The tracing from the left frontomotor (*F.M.*) lead shows irregular delta activity.

2/23/45: Twenty-four weeks after operation. Contralateral seizures were elicited. Abnormal electroencephalographic activity is present bilaterally, being predominant on the left side.

6/1/45: Thirty-eight weeks after application of the agent, or one week preceding onset of generalized convulsions. Electroencephalographic abnormality is increased, being more pronounced on the left.

7/14/45: Forty-five weeks after application of the agent. Generalized convulsions were present. The tracing shows pronounced abnormality, especially persistent on the left, with a greater incidence of sharp formations.

Observations.—The clinical and electroencephalographic observations are recorded in table 1, and representative electroencephalograms are shown in figures 1 and 2. It may be seen in general that within five weeks after operation the electroencephalogram revealed a focus of abnormality consisting chiefly of delta activity, random spikes and sharp formations about the site of application of the alumina cream.⁴ At the same time, or shortly thereafter, abnormality in the electroencephalo-

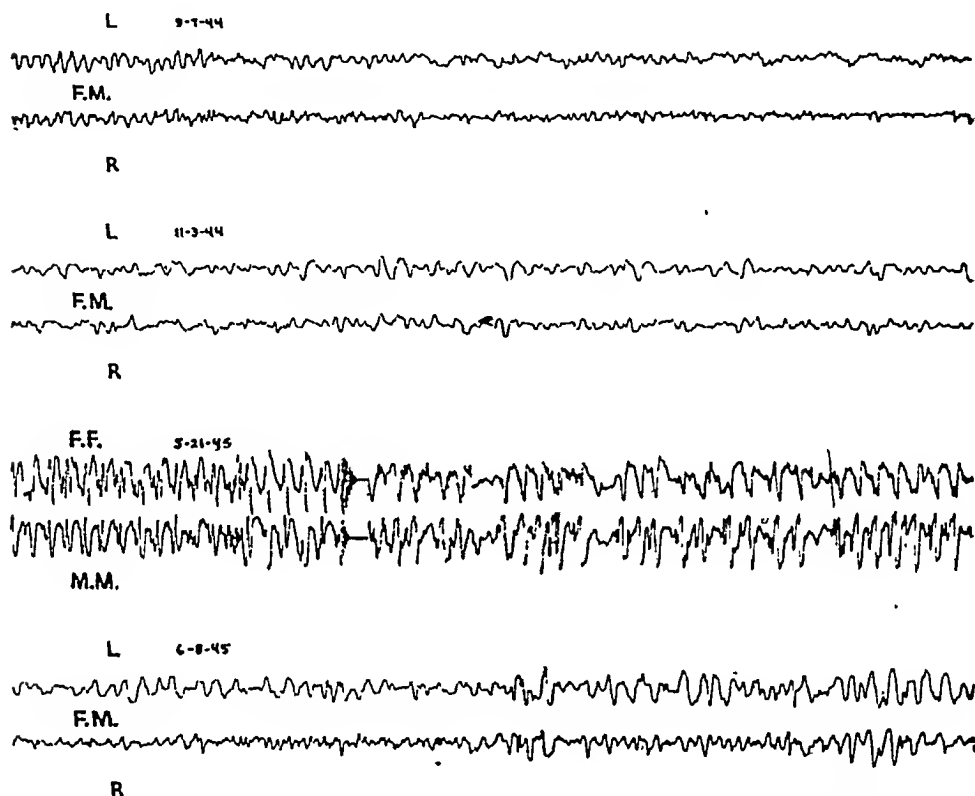


Fig. 2 (monkey 450)—9/7/44: Control tracing prior to operation, taken with bilateral frontomotor leads (F.M.), showing normal activity, with frequent trains of alpha rhythm and some low voltage fast activity.

11/3/44: Eight weeks after application of the active agent to the left precentral cortex. No clinical seizures were observed. The left frontomotor (F.M.) lead shows irregular delta activity; the right, irregular features and occasional slow waves.

5/21/45: Thirty-seven weeks after application of the agent, and two weeks preceding onset of generalized convulsions. Contralateral seizures were elicited. The transfrontal (F.F.) and frontomotor (M.M.) leads show frequent bursts of spike and dome activity.

6/8/45: Thirty-nine weeks after operation. General convulsions occurred. Abnormal activity (delta waves and random spike potentials) is present, being more pronounced on the left. Discharges of spike and dome activity are not present, but frequent trains of serial slow rhythm are noted.

4. "Alumina cream was prepared by adding a slight excess of 1 per cent solution of ammonium hydroxide at room temperature to a 1 per cent solution of ammonium alum (ammonium aluminum sulfate) and the resulting precipitate washed by decantation until only traces of sulfate remained in the supernatant fluid."^{1a}

graphic pattern appeared in the corresponding region of the opposite side. These abnormalities increased in degree for a number of months and usually reached a maximum in twenty-four weeks. In 1 instance this occurred in seventy weeks and in another in two hundred and thirteen weeks. Although increasing electroencephalographic abnormality was noted on both sides, it was relatively greater on the side of application of the inciting agent. In 2 monkeys the abnormality had become approximately the same on the two sides after fifty-four and sixty-one weeks, respectively. The maximal electroencephalographic disturbance persisted for varying periods, from three to twenty-nine weeks, in 4 monkeys (449, 450, 451 and 452) on which extended observations were made. In control animals (453 and 454) to which rare earth oxides, instead of aluminum compounds, had been applied, clinical seizures could not be elicited, and electroencephalograms revealed no abnormalities during the sixty-one week period of observation (fig. 3).

A relationship between electroencephalographic abnormality and the manifestation of convulsive seizures may be seen from the data in table 1. In all monkeys electroencephalographic abnormality preceded the onset of seizures. With minimal disturbances in the electroencephalogram, seizures were almost always confined to one side of the body. With increasingly abnormal electroencephalographic activity, convulsions became generalized and could readily be elicited over a period of several months. When the electroencephalographic abnormality decreased, the seizures were confined to one side. In 1 instance (monkey 449) in which occasional seizure-free periods occurred, evidence of focal abnormality was still present.

The effect of ablation of a focus induced by alumina cream was studied in 2 monkeys (451 and 452). Generalized convulsions had been elicited by physical stimulation over a period of twenty-three and twenty-two weeks, respectively, after which the disks were removed and area 4 of the original focus was ablated by cauterization (monkey 451) or suction (monkey 452). During the succeeding seven weeks generalized convulsions were elicited intermittently in monkey 451. At the end of the tenth week contralateral jacksonian seizures only were observed. Subsequently, no convulsive manifestations could be induced. During the postablation period the electroencephalogram showed a gradual diminution in the degree of abnormality, with only slight delta activity in the region of the original focus after the tenth week. By the twenty-seventh week delta waves had disappeared (table 1 and fig. 4). In monkey 452, no convulsive manifestations could be elicited after ablation, despite a generally abnormal electroencephalographic record. Within six weeks after ablation the electroencephalogram showed gradual diminution and eventual disappearance of delta activity. It should be stated that in monkey 452 the ablation was extended beyond area 4

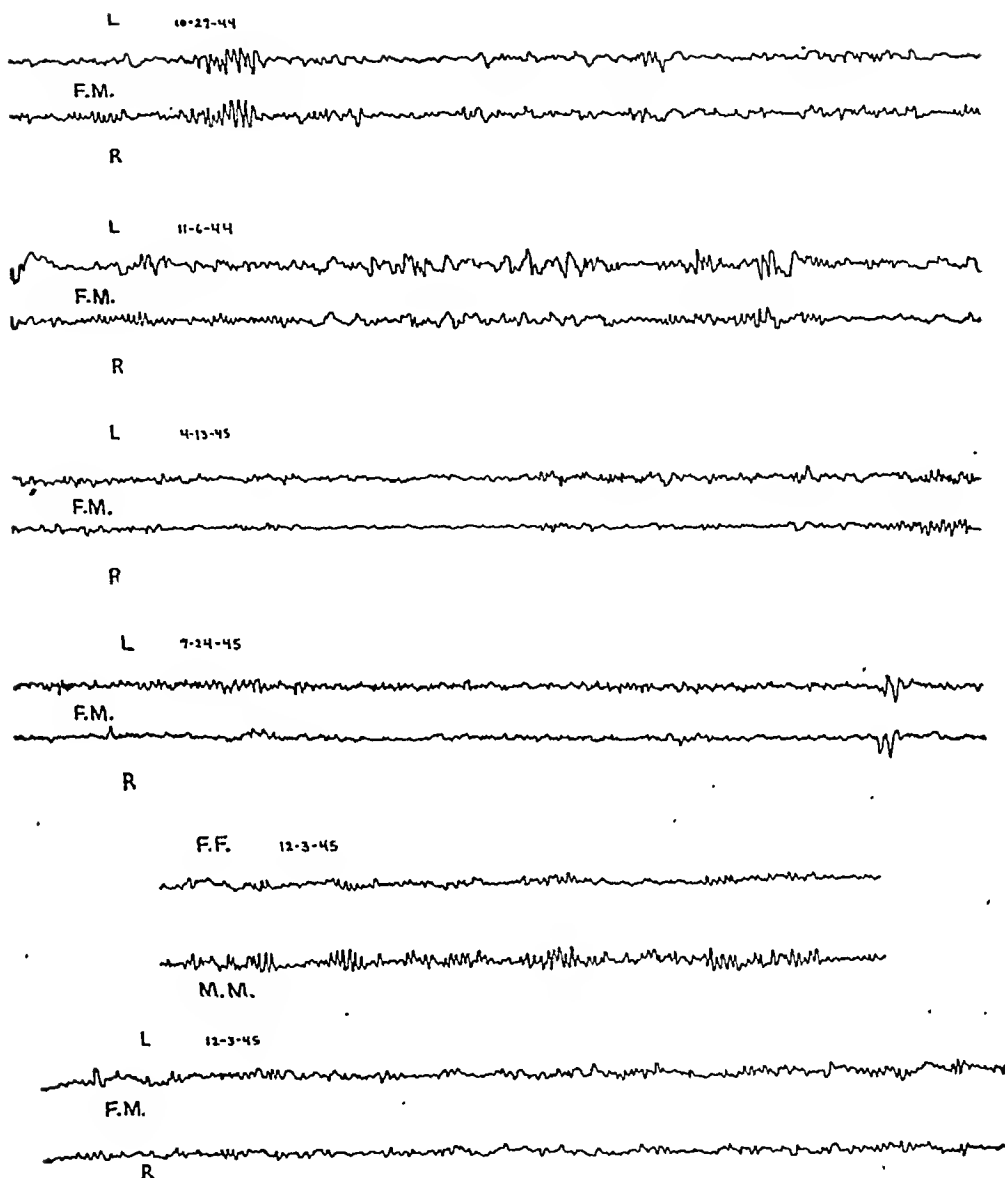


Fig. 3 (monkey 454; control animal).—10/27/44: Four weeks after application of an inactive agent (rare earth oxides) to the left precentral cortex. No clinical seizures were present. There are no electroencephalographic abnormalities or significant differences between the two sides.

11/6/44: Six weeks after application of the inactive agent. No seizures were elicited. The electroencephalographic pattern is similar to that shown in the preceding tracing.

4/13/45: Twenty-eight weeks after application of the agent. No seizures were observed. No electroencephalographic abnormalities are present.

7/24/45: Forty-three weeks after operation. There were no seizures. No electroencephalographic abnormalities are present.

12/3/45: Sixty-one weeks after operation. No seizures occurred. No electroencephalographic abnormalities or significant differences between the two sides are observed.

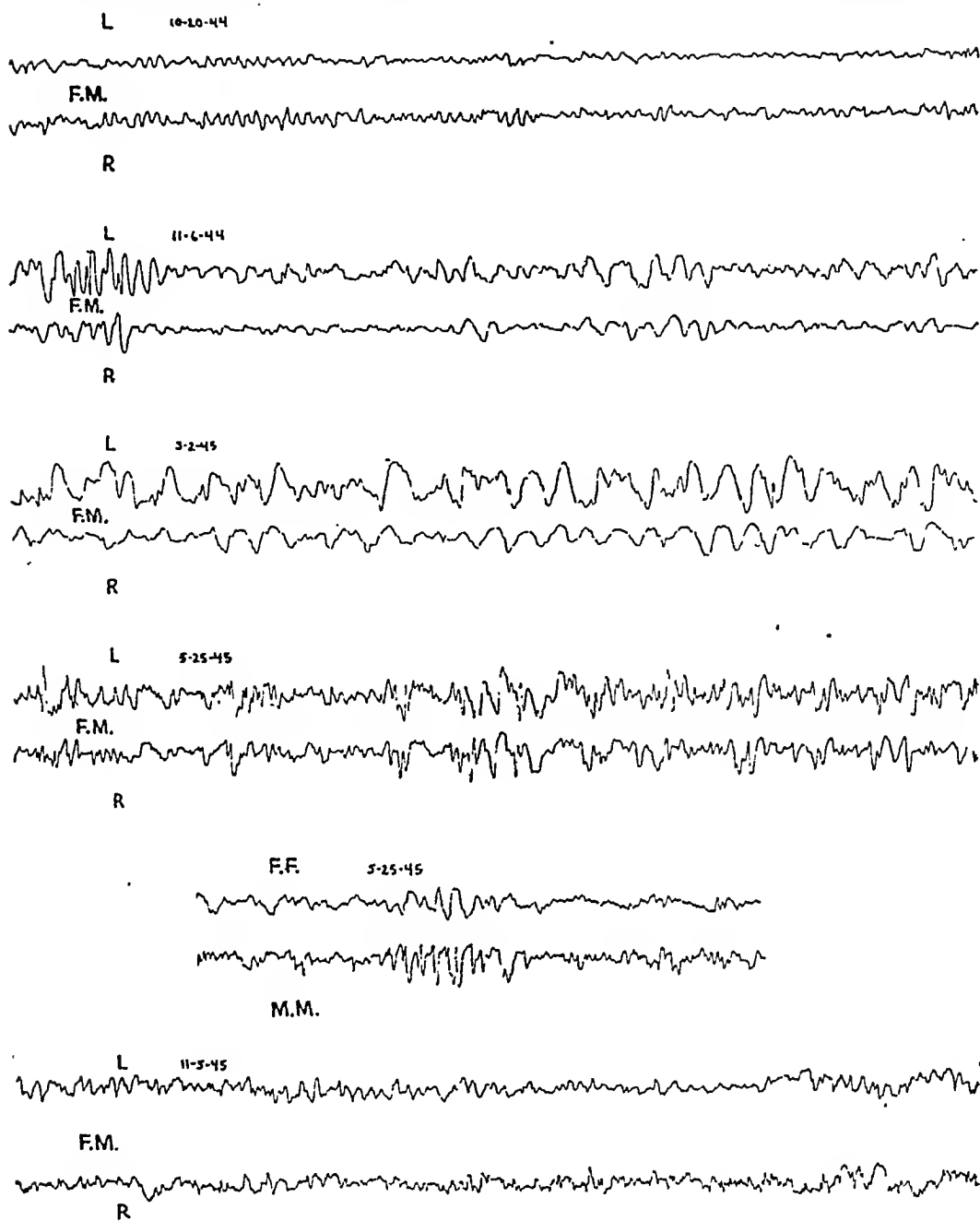


Fig. 4 (monkey 452).—10/20/44: Tracing five weeks after application of the active agent to the left precentral cortex. There were no clinical seizures. Beginning electroencephalographic disturbances are obtained from the left side.

11/6/44: Eight weeks after operation. Contralateral seizures were elicited. Frequent bursts of slow activity and spike and dome discharges appear on the left. Bursts of slow activity are also present on the right, with relatively diminished amplitude, but no spike potentials.

3/2/45: Twenty-four weeks after operation, and seven weeks before generalized seizures were observed. Frequent serial delta activity is present on the left, with random spike potentials. Serial slow activity, of lower amplitude and without spike formation, is present on the right.

5/25/45: Thirty-six weeks after operation. Generalized convulsions were present. Increased fast activity, frequent spike potentials and random spike and dome complexes are present bilaterally, being more pronounced over the left precentral cortex.

11/5/45: Sixty weeks after application of the active agent, or five and one-half weeks after ablation of area 4 of the left side. No clinical seizures occurred after ablation. The electroencephalographic disturbance is greatly decreased, with frequent trains of alpha rhythm, occasional slow potentials and low voltage sharp formations.

into area 6 approximately 1 mm. and the anterior border of the post-central gyrus undermined approximately 2 mm. This more extensive ablation may have removed more motor cells and more of the focal zone than was ablated in monkey 451, and may well account for the abrupt cessation of seizures and the more rapid diminution of abnormal electroencephalographic activity in this monkey. In a control animal (monkey 430), which had received applications of zinc oxide to the left motor cortex, with no convulsive manifestations, for seventy-two weeks, the disk was removed and area 4 electrocauterized. The electroencephalogram showed no persisting abnormality either one week before or forty-three weeks after cauterization (fig. 5).

It seemed of interest to determine whether any significant differences in convulsive reactivity to metrazol existed between animals exhibiting chronic convulsive seizures and others which had been similarly prepared with nonepileptogenic materials. A further comparison was made with monkeys of both types in which ablation of area 4 had been performed. Also included were 1 monkey in which alumina cream had been applied to the area underlying the ablated motor cortex, 1 monkey in which only areas 4 and 6 on one side had been ablated, and 6 monkeys without operation. Clinical epileptic seizures had never been elicited in the monkeys prepared with nonepileptogenic substances or after surgical ablation of the previously treated motor cortex. Intravenous injections of 10 per cent metrazol were administered to each monkey in graduated daily doses until the limiting convulsant dose was established. The results are presented in table 2. It may be seen that in all animals in which alumina cream had been applied to the precentral cortex or to the underlying subcortical tissue, the limiting convulsant dose of 10 per cent metrazol was below 0.25 cc. Similar results were obtained in those monkeys which had received alumina cream over the precentral cortex and in which the subsequent ablation of the treated area had resulted in cessation of convulsive seizures. However, it is likely that some alteration of the cellular elements (motor cells outside area 4) surrounding the original focal zone or the area of ablation may have been responsible for the persistence of the lowered threshold observed. More extensive ablations into the prefrontal and anterior parietal zones are contemplated. The critical convulsant dose of metrazol for the 3 monkeys prepared with nonepileptogenic substances (in 1 of which the motor cortex had been ablated), or for the animal in which only ablation of the motor cortex had been performed, or for untreated monkeys was found to be between 0.4 and 0.6 cc. Therefore, it is evident that alumina cream caused a lowering of the convulsive threshold to metrazol even when clinical seizures had been eliminated or prevented by surgical ablation of the precentral cortex.

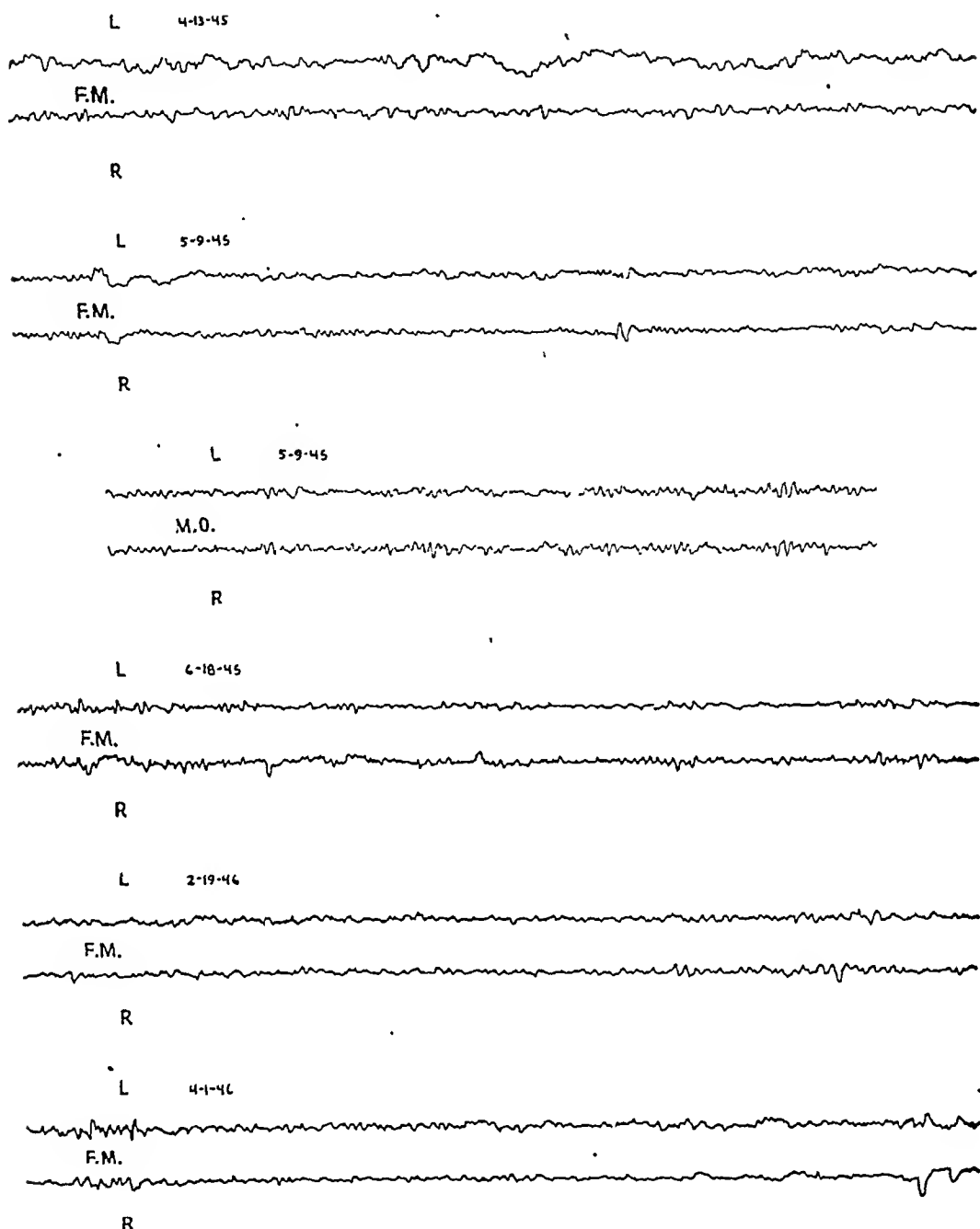


Fig. 5 (monkey 430, control animal).—Tracing seventy-one weeks after application of an inactive agent (zinc oxide) to the left precentral cortex. No clinical seizures were observed. Ablation of area 4 of the left side was performed on April 20.

5/9/45: Seventy-five weeks after application of the agent, and three weeks after ablation. No seizures were observed. No electroencephalographic abnormalities are present (*M.O.* indicates motor occipital area).

6/18/45: Eighty-one weeks after application of the agent, and nine weeks after ablation. No seizures were observed. No electroencephalographic abnormalities are present.

2/19/46: One hundred and sixteen weeks after application of the agent and forty-four weeks after ablation. No seizures were observed. No electroencephalographic abnormalities are present.

4/1/46: One hundred and twenty-two weeks after application of the agent, and fifty weeks after ablation. No seizures were observed. No electroencephalographic abnormalities are present.

TABLE 2.—Critical Convulsant Dose of 10 per Cent Metrazol

Monkey No.	Date	First Operation	Date	Epileptogenic Material	Second Operation	Convulsive Seizures	Minimal Intravenous Convulsant Dose of Metrazol, Cc.*
449	9/ 8/44	Alumina cream, ⁴ motor cortex				+	0.05†
457	1/10/45	Alumina cream, ⁴ motor cortex				+	0.20
451	9/15/44	Alumina cream, ⁴ motor cortex	5/16/45		Ablation of motor cortex	++	0.25
452	9/15/44	Alumina cream, ⁴ motor cortex	10/ 2/45		Ablation of motor cortex	++	0.15
420	11/23/43	Ablation of motor cortex; alumina cream applied subcortically				..§	0.20
Nonleptogenic Material							
453	9/29/44	Rare earth oxides, motor cortex				0	0.50
451	9/29/44	Rare earth oxides, motor cortex				0	0.50
430	11/30/43	Zinc oxide, motor cortex	4/18/44		Ablation of motor cortex	0	0.60
487	12/ 4/45	Ablation of motor cortex				0	0.50
Controls Not Operated On							
486						0	0.50
497						0	0.60
500						0	0.40
502						0	0.40
503						0	0.60
504						0	0.40

* The minimal convulsant dose of 10 per cent metrazol, the approximate threshold value, was determined after repeated trials (April 22 to June 7, 1946).
† Lowest dose tested.
‡ Before ablation.

§ One short clonic seizure of the right leg only (March 14, 1944).

SUMMARY

1. In rhesus monkeys the application of alumina cream to the motor cortex on one side produced a primary focus of electroencephalographic abnormality, characterized chiefly by delta activity, random spikes and sharp formations. This abnormality appeared prior to the onset of jacksonian attacks, which could be elicited by physical stimulation. Subsequently, a secondary (mirror) focus of electroencephalographic abnormality developed in the opposite motor cortex, which was followed later by generalized convulsions.

2. A direct correlation was found between the degree of electroencephalographic abnormality and the convulsive threshold. Maximal electroencephalographic disturbance was usually associated with generalized convulsions. Minimal electroencephalographic abnormality was associated with jacksonian attacks and was also present after the cessation of seizures.

3. Ablation of area 4 resulted in eventual cessation of seizures and diminution of electroencephalographic abnormalities.

4. The limiting intravenous convulsant dose of metrazol for monkeys exhibiting epileptic seizures, or for similarly prepared monkeys after ablation of the primary focus, or for a monkey in which alumina cream had been applied subcortically, was significantly lower than that for control monkeys.

Miss Mary Szczerba, Mr. Benjamin Blattberg, Miss Judith Darmstadter and Mr. Kurt Lopez gave technical assistance.

722 West One Hundred and Sixty-Eighth Street.

INVESTIGATIONS ON NARCODIAGNOSIS

F. A. FREYHAN, M.D.

FARNHURST, DEL.

ONE of the essential problems in psychopathology is that of differentiation between primary and secondary determinants of abnormal mental states. Reduction of various clinical symptoms to a point where one group of characteristics finally emerges as the supposedly specific pathologic nucleus of a clinical entity led to the development of the concept of the "fundamental disturbance." Bleuler,¹ representing the Swiss school; Berze,² Birnbaum,³ Küppers⁴ and Kronfeld,⁵ the German school, and Minkowski⁶ and Claude,⁷ the French school, are the main investigators of this subject. It was Claude who, in 1924, reported a new method which he believed to be experimental and objective. He selected negativistic schizophrenic patients, anesthetized them with ether and observed the changes in attitude which some of the patients displayed as they passed from consciousness into a state of narcosis. He concluded that patients who showed no changes at all suffered from a physiogenic disturbance, whereas patients who started to talk and respond had a psychogenic disturbance. In a way, this method can be called a forerunner of the sodium amytal interview. The differences between Claude's etherization method and the intravenous use of barbiturates are pharmacologic as well as conceptual. Claude intended to study the structure of psychoses in regard to determinants,

*Read at the annual convention of the American Psychiatric Association, Chicago, May 28, 1946.

1. Bleuler, E.: Textbook of Psychiatry, New York, The Macmillan Company, 1924; The Physiogenic and Psychogenic in Schizophrenia, *Am. J. Psychiat.* **10**:203, 1930.

2. Berze, J., and Gruble, H. W.: Psychologie der Schizophrenie, Berlin, Julius Springer, 1929.

3. Birnbaum, K.: Kriminal-Psychopathologie, Berlin, Julius Springer, 1921.

4. Küppers, E.: Ueber den Begriff der Grundstörung und seine Bedeutung für die Einteilung und die Lokaldiagnose der Geisteskrankheiten, *Arch. f. Psychiat.* **99**:1, 1933.

5. Kronfeld, A.: Perspektiven der Seelenheilkunde, Leipzig, Georg Thieme, 1930.

6. Minkowski, E.: Du symptôme au trouble générateur (Quelques réflexions sur la psychopathologie contemporaine), *Schweiz. Arch. f. Neurol. u. Psychiat.* **22**:35, 1928.

7. Claude, H.; Borel, A., and Robin, G.: Un nouveau procédé d'investigation psychologique; l'étherisation, *Encéphale* **19**:419-421, 1924.

which he conceived to be either organic or psychogenic. The question arises how the more perfected use of the narcotic method of today can be utilized for investigations into the structure of psychopathologic states.

Psychopharmacologic studies with sodium amytal by Lindemann,⁸ Thorner⁹ and others have revealed that the effect of the drug is anti-inhibitory. The interpretation of revealed contents depends essentially on concepts of personality structure. There is general agreement on the existence of forces within the personality which are not in the sphere of consciousness. Considerable diversity of opinion exists in regard to the nature of these forces. The problem of personality structure has a direct bearing on the utilization of the sodium amytal method. Lorenz¹⁰ and Bleckwenn¹¹ reported observations on catatonic patients who while under the influence of sodium amytal showed changes from negativistic to responsive attitudes. These authors concluded that the psychosis, while being at a much lower level of mental existence than the normal, was not as deep as real unconsciousness. Precipitation into unconsciousness, therefore, would pierce through the level of catatonic stupor and dislodge the catatonic mechanism. Gottlieb and Hope¹² found sodium amytal to be a distinct aid in evaluation of the prognosis. They estimated the degree of preservation of personality by the extent to which the patient's behavior, under the influence of the drug, approached normal. The goal of the sodium amytal method becomes the uncovering of the more intact portions of the ego. These concepts, however, meet with certain difficulties. A schizophrenic patient, for instance, whose catatonic rigidity and mutism disappear under the influence of the drug does not really approach normal, but remains just as unrealistic and autistic in his general orientation as before. One must conclude, therefore, that the pathologic process affects the entire personality rather than isolated levels. It is this situation which necessitates differentiation between fundamental factors, an autistic and unrealistic orientation, for instance, and secondary phenomena, such as motor disturbance and mutism. Rigid concepts, dividing the personality into

8. Lindemann, E.: The Psychopathological Effects of Sodium Amytal, *Proc. Soc. Exper. Biol. & Med.* **28**:864, 1931; Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, *Am. J. Psychiat.* **11**:1083, 1932.

9. Thorner, M. W.: The Psycho-Pharmacology of Na-Amytal, *J. Nerv. & Ment. Dis.* **81**:161, 1935.

10. Lorenz, W. F.: Some Observations on Catatonia, *Psychiatric Quart.* **4**:95-102, 1930.

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12. Gottlieb, J. S., and Hope, J. M.: Prognostic Value of Intravenous Administration of Sodium Amytal in Cases of Schizophrenia, *Arch. Neurol. & Psychiat.* **46**:86-97 (July) 1941.

certain strata, interfere with maintaining the perspective of the total personality, especially in the case of pathologic changes which are fundamental and affect the personality in its entirety.

The aim of the present investigation is to study the qualitative aspects of the responses for a phenomenologic evaluation of determinants of symptom formation. For the purpose of this investigation, I shall advance a definition of these phenomena according to which fundamental factors express themselves as pathologic tendencies in general personality function, whereas secondary phenomena are to be attributed to subjective inner experiences. The interrelationship of these phenomena will be examined in the light of the actual observations, and interpretations will be based on the facts as they present themselves.

REPORT OF STUDY

The 56 patients selected for this investigation had previously been under my observation. Their behavior pattern as well as their past and present problems had been studied carefully. Thorough knowledge of a patient's personality must be considered a prerequisite for this use of the narcotic method, as it is otherwise impossible to gain an accurate impression of changes which occur in the state of altered consciousness.

Although it would be desirable to consider each patient individually, the brevity of this report demands that observations be classified according to types of responsivity. The common denominator of each response group is based on the phenomenologic aspects of the reaction and does not concern psychopharmacologic evaluations. Three groups, *A*, *B* and *C*, based on responsivity to the drug were established. Group *A* comprises patients who show striking changes in the disclosed thought content, as well as in general attitude. These patients revealed thought material previously unknown and assumed attitudes which were in contrast to those observed prior to the injection of sodium amytal. In group *B* were placed patients whose reactions differed from their usual behavior pattern through more willingness to communicate and change in emotional tone, whereas the expressed thought contents remained essentially uninfluenced. Group *C* consisted of patients who did not manifest psychologic changes. The content of thought and the emotional behavior pattern remained uninfluenced. The same technic of administering sodium amytal was used with all patients. The injection was given while the patient lay relaxed on a bed. The dose varied from 5 to 15 grains (0.975 to 0.325 Gm.), given as a 5 to 10 per cent solution. Each interview was started with the beginning of the injection, and the needle was held in the vein until the patient had reached and maintained a satisfactory state of narcosis.

Case Material.—The diagnostic classification of the 56 patients, taken from the hospital records, is as follows:

1. Schizophrenic, 31 patients; paranoid, 14; catatonic, 13; hebephrenic, 2, and simple, 2.
2. Affective disorder, 14 patients: manic type, 3; depressive, 6; involutional, 5.
3. Organic psychosis, 3 patients; dementia paralytica, 2; epilepsy with clouded states, 1.
4. Personality disorders without psychosis, 8 patients: psychopathic personality, 2; alcoholism, 3; simple maladjustment, 2 and conversion hysteria, 1.

RESPONSE GROUPS

GROUP A.—Of the 18 patients in this group, 5 had affective disorders; 9, schizophrenia; 1, an organic psychosis, and 3, minor type of personality disorders.

The brevity of this report does not permit description of the patients' reactions; suffice it to say that remarkable changes were observed. One catatonic patient, who had been mute and akinetic, danced, talked and even imitated himself. Another catatonic patient, also mute and rigid, stated during the interview: "It is not proper for me to talk; I have no power to change my posture; the injection broke the tissues down and made me able to talk to you." A man in a depressed stupor became agitated and experienced the torture of seeing his wife having intercourse with hundreds of sailors.

GROUP B.—Of the 16 patients in this group, some showed greater willingness to talk; others displayed a friendlier and more emotionally accessible attitude, but none of them disclosed any new thought content. These patients included 3 with affective disorders; 1 with a manic and 2 with a depressive psychosis; 8 with schizophrenic disorders, including 4 with the paranoid, 2 with the catatonic, 1 with the simple and 1 with the hebephrenic type; 1 with an organic disorder, dementia paralytica, and 4 with minor disorders, 2 being maladjusted, 1 psychopathic and 1 alcoholic.

A manic patient, for instance, who talked incessantly but had been rather hostile and aggressive toward the physician, became friendly and flirtatious under the influence of the injection, but continued to talk in her usual fashion. Depressed patients showed an increased ability to keep up conversation; paranoid patients were more accessible and showed less hostility and agitation, but expressed their usual delusions.

GROUP C.—This group consisted of 22 patients. Their psychologic reactions lacked significant change, as they remained uninfluenced in their attitude and in the expressed thought contents. The group included 6 patients with affective disorders, 1 of whom had a manic and 5 a depressed psychosis; 14 with schizophrenic disorders, 6 of whom had the paranoid, 6 the catatonic, 1 the simple and 1 the hebephrenic type; 1 with an organic disorder, epilepsy with a paranoid tendency and clouded states, and 1 with a minor disorder, alcoholism.

COMMENT

Analysis of the phenomenologic aspects of these data indicates, first, the absence of correlations between diagnostic categories and types of responsivity; all types of mental disorders are represented in each of the three groups. Comparison of the groups in regard to the number of patients reveals 18 in group A, 16 in group B and 22 in group C.

This means that only a relatively small part manifested a significantly changed attitude, while the greater part showed only moderate changes or were not influenced by the treatment. This observation is interesting in view of the fact that the phenomenon of "lack of change" has been somewhat neglected in the literature on the method. Many investigators have evaluated selected responses, which were perhaps characteristic of certain mental disturbances, and have generalized their interpretations in conformity with dynamic preconceptions. A critical appraisal of the diversity of reactions does not support the frequently expressed opinion that the deeper levels of the personality begin to speak according to the depth of narcosis and that repressed and unconscious material comes freely to the surface. This claim is based on the belief that the unconscious system represents a regular level or space within the personality structure, a hypothesis which, as must not be forgotten, is not to account for neurotic symptoms only, but to have universal validity and to throw light on normal and abnormal mental functioning. It is difficult to understand how conceptions of unconscious forces within the personality can be so spatial, so architectural in nature as to permit the establishment of an equation according to which depths of narcosis correspond to certain levels of personality. To understand the significance of the diversity of responses, one must maintain the perspective of a total personality. An altered state of consciousness as induced by the drug can represent neither personality levels nor a realm of autonomous dynamisms. The assumption that repression is a prerequisite of symptom formation finds little support in the data of this study. Removal of inhibitory influences failed to change the phenomenologic aspects of symptoms of 22 patients in group C and of 16 in group B, who, whatever changes they showed, did not reveal thought contents which could be traced to sources of which the patient was not conscious. Of the 18 patients in group A who did manifest striking changes, some revealed material which had been consciously subjugated, and others expressed inner experiences which were not within the sphere of consciousness.

A qualitative evaluation of the various types of response enables one to discern and to understand in what manner the symptoms depend on totally altered personality function and to what extent they are influenced by subjective experiences. This will be more clearly understood as one examines some of the responses. One of the mute catatonic patients, for instance, disclosed during the interview that he did not talk because voices would creep into his mouth and emerge through his ears. Another catatonic patient stated he had to maintain one posture and could not talk because it would be "improper" for him to do so. Both cases show how the symptom of muteness and postural stereotypy is determined by certain inner experiences. These determinants are

secondary and can be understood only through recognition of the fundamental disturbance, which affects the person's entire orientation. The actual determinants of muteness and motor passivity in these 2 patients, however, were psychologic. These findings may be contrasted with observations on patients in depressed stupor who failed to manifest changes under the influence of the drug. They, too, showed muteness and motor passivity. Here, however, the symptoms seemed to be caused by a fundamental retardation in personality function, which affected motor, intellectual and emotional activities alike. If intentionality is totally impaired or altered, clouding of consciousness does not affect the phenomenologic nature of symptoms. The clinical importance of the recognition of primary and secondary determinants can be demonstrated in the case of a patient with neurosyphilis. This good-looking, middle-aged woman responded well serologically but became increasingly preoccupied and negativistic. She shaded her eyes with her hands while walking around and ignored her environment completely. While under the sodium amytal narcosis, she talked with a friendly and soft voice; she indicated that she could not pay any attention to her environment, as she had to concentrate all her attention on listening to the voice of her husband. (The patient's husband had left her after he learned the nature of her illness.) She denied emphatically that she worried about her husband's attitude, saying that he was hers as long as she could hear him talking to her. The narcodiagnostic method in this case revealed that certain symptoms of her psychosis were caused by inner experiences which enabled her to remain close to her husband. These symptoms of her psychosis could not be attributed simply to the fundamental, in this case organic, factor, but were determined by secondary formations, which represented her way of adjusting to the marital situation.

It is outside the scope of this investigation to examine the complex nosologic and etiologic aspects of primary and secondary determinants. Claude oversimplified the interpretation of his etherization method, for he declared determinants to be either psychogenic or organic. The briefly outlined evaluation of observations in this investigation shows that a phenomenologic analysis of fundamental and secondary factors can contribute to one's knowledge of determinants and symptom formation. One seems justified, therefore, in concluding that the narcotic method has potentialities as an instrument for psychopathologic investigations.

Delaware State Hospital.

POSTOPERATIVE PERIOD OF SURVIVAL OF PATIENTS WITH OLIGODENDROGLIOMA OF THE BRAIN

Report of Twenty-Five Cases

HENRY A. SHENKIN, M.D.

FRANCIS C. GRANT, M.D.

AND

JOHN H. DREW, M.D.

PHILADELPHIA

OF THE intracranial gliomas, the group described as the oligodendrogliomas has been considered relatively benign. Since these tumors infiltrate the surrounding brain, complete removal may be impossible; yet recurrent symptoms have been reported only after a lapse of three to five years. Recently, however, this point has been questioned.¹ In an attempt to throw further light on the matter, we have reviewed the clinical course in 25 cases of verified oligodendrogliomas in the files of the neurosurgical laboratory of the Hospital of the University of Pennsylvania.

PRESENT INVESTIGATION

In 6 of the 25 cases in this series (24 per cent) the tumor was intraventricular, presumably arising from the walls of the ventricle. In 2 cases the tumor lay wholly within one of the lateral ventricles—in 1 case in the right and in the other in the left. The third ventricle appeared to be the original site of growth in 4 cases, the tumor spreading through the foramens of Monro into both lateral ventricles in 2 cases and into the right lateral ventricle only in the other 2 cases. These tumors were all solid growths, 3 of which were visualized before operation because of calcification within the tumor. No basis for histologic differentiation of this type of oligodendroglioma could be deduced.

In the remaining 19 cases the tumor was classified as the intra-hemispheric type. In 4 of these cases the tumor, while growing chiefly in the substance of the cerebrum, extended nevertheless into the lateral

From the Departments of Neurosurgery and Neuropathology of the Hospital of the University of Pennsylvania.

1. (a) Eisenhardt, L.: Long Postoperative Survivals in Cases of Intracranial Tumor, *A. Research Nerv. & Ment. Dis., Proc.* (1935) **16**:390-416, 1937.
(b) Elvidge A.; Penfield, W., and Cone, W.: The Gliomas of the Central Nervous System, *ibid.* **16**:107-181, 1938.

ventricles. It is interesting to note that in 4 other cases of this group the tumor, when first visualized at operation, appeared to be extra-cerebral and was thought to be a meningioma. However, when the discrete surface of the tumor was dissected free, it was noted that the base of the growth arose from the brain substance, and only at this point did its gliomatous nature become clear. Oligodendrogliomas of this type, again, showed no histologic differentiation from the more obviously infiltrating type. The appearance was generally described as soft, reddish and vascular. Occasionally it was noted that the tumor was, in addition, granular and friable. In several instances the surrounding white matter was unusually hard, and histologic sections of this area showed considerable reactive gliosis of the parenchyma about the tumor. In almost all instances in which sufficient material was available the zone of growth of the tumor was extremely narrow.

In 8 of the cases of the intrahemispheric type the tumor was located in the right frontal area, and in 4, in the left frontal area. In 4 cases the growth occurred in both frontal areas, being predominantly in one or the other hemisphere in 3 cases and being equally distributed in the two frontal lobes in 1 case. In 3 cases the tumor was located in the left parietal lobe. These data emphasize the predominant frontal localization of the oligodendrogliomas.

In 13 of the 25 cases the tumor was sufficiently calcified to be recognized in the preoperative roentgenogram. In 5 other cases calcification was described in the histologic preparation only. The calcification was noted to be related primarily to the blood vessels.

None of the tumors of the ventricular type was cystic, but 5 of the remaining 19 oligodendrogliomas in this series contained definite cystic areas. In no instance was cyst formation predominant throughout the tumor. In 1 instance the cysts were recognized only microscopically.

Histologically, the tumors revealed the characteristics described by Bailey and Cushing² and amply confirmed by later authors.

Clinical Features.—Tumors of the ventricular type occurred at a significantly earlier age than did those of the hemispheric type. The ages of the patients with the ventricular type averaged 25 years, with a range of 19 to 29 years. The ages of the patients with the hemispheric type averaged 37 years, with a range of 21 to 58 years. The series was almost equally divided as to sex, with 12 women and 13 men.

In the 6 cases of ventricular tumor the average preoperative period was seven and two-thirds months, with a range of three to eleven months. The early symptoms were those of increased intracranial pressure. Focal signs were generally absent, or, if present, appeared late in the course

2. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

of the disease. Convulsive seizures did not occur before operation in this group, although in 2 of the 6 cases there occurred attacks of decerebrate rigidity, caused by recurrent crises of increased intracranial pressure.

The preoperative duration of symptoms in the 19 cases of intrahemispheric tumor averaged thirty-five months, with a range of five to one hundred and four months. The onset of symptoms in 9 cases was with focal neurologic signs and epileptic seizures. The latter were of jacksonian nature in 7 cases and were generalized in 2 cases. In 6 of these 9 cases symptoms of increased intracranial pressure later developed. The initial symptoms in the 10 remaining cases were those of increased intracranial pressure. In 9 of these 10 cases focal symptoms and signs of the cerebral lesion appeared later in the course of the disease and in 3 cases epileptic seizures occurred.

It is thus evident that in 12 of the 19 cases of intrahemispheric tumor epileptic seizures occurred prior to operation.

Course and Prognosis.—The average postoperative life span of 20 patients was twenty-one months. Of this group, 4 are still alive, ten to fifty months after operation. Five patients in our series (20 per cent) died in the immediate postoperative period.

Ventricular Group: One patient died on the first postoperative day. He had had symptoms of thirteen months' duration, the predominant feature of which in the last few months of his life was repeated episodes of decerebrate rigidity. The tumor was located in the third ventricle and had extended into each of the lateral ventricles.

One patient is still alive, fifty months after her first operation. She had a recurrence of symptoms of increased intracranial pressure requiring a second operation seven months after the initial procedure. The tumor, located in the left lateral ventricle, was thought to have been completely removed at the second operation. She is now asymptomatic, does all her own housework and is successfully raising a family. She was not given radiation therapy at any time.

The 4 remaining patients with ventricular tumors had survival periods of two, three, twenty-two and twenty-three months, respectively, with an average of twelve and one-half months. One of these patients had three courses of intensive radiation therapy, without apparent effect on the course of the disease. None of these patients had epileptic seizures after operation, and all died of recurring symptoms of increased intracranial pressure.

Intrahemispheric Type: There were 4 postoperative deaths in the series of patients with oligodendroglioma infiltrating the cerebrum. Four patients are still alive, thirty, fifteen, ten and ten months after operation. None of the latter is fully capable. Two are physically well but mentally incapable of holding a job and, in addition, have occasional epileptic

seizures, although these are generally well controlled with medication. One patient has a residual hemiplegia and exhibits serious personality changes. The last of this group, who still survives, is mentally intact and has no residual neurologic disturbances other than total blindness, which was present before operation and was due to severe papilledema. The remaining 11 patients survived an average of twenty-two months, the periods ranging from five to forty-eight months. However, the patients whose tumor extended outside the cortex had a distinctly longer period of survival (thirty-two months) than the patients whose tumor was limited to the brain substance (eighteen and one-half months).

Four patients in this group had a second operation for recurrence of symptoms anywhere from one to two years after the original procedure. All died within six to eight months after the second exploration. Two of this group died of intercurrent disease, without evidence of recurrence of symptoms of the cerebral tumor. One died of carcinoma of the pancreas sixteen months after operation, and 1, of acute ascending myelitis (verified at autopsy) forty-five months after operation. Histologic examination of the brain at necropsy did not reveal recurrence of the cerebral tumor. Nine of these 11 patients had convulsive seizures after operation; 2 died in status epilepticus—1, eight and 1 nineteen months after operation. Abrupt cessation of anticonvulsant therapy was the immediate cause of the status epilepticus.

COMMENT

The predisposition of oligodendrogliomas to grow within the ventricle was remarked on by Greenfield and Robertson.³ A few years later, Löwenburg and Waggoner⁴ emphasized this point and reported that the growth of the oligodendroglioma in 2 cases, in a series of 21, was largely confined to the ventricles. Of our entire series, the oligodendroglioma could be classified as the ventricular type in 24 per cent. Our observations further confirmed the experience of Löwenburg and Waggoner,⁴ namely, that the frontal lobes are the favored site of growth of this type of glioma and that there is a distinct tendency of the growth to spread from one hemisphere to the other across the midline, through the corpus callosum.

From the results of this study, we were unable to confirm recent reports⁵ that there is a tendency of oligodendrogliomas to disseminate

3. Greenfield, J. G., and Robertson, E. G.: Cystic Oligodendrogliomas of the Cerebral Hemispheres and Ventricular Oligodendrogliomas, *Brain* **56**:247-264, 1933.

4. Löwenburg, K., and Waggoner, R. W.: Gross Pathology of the Oligodendrogliomas, *Arch. Neurol. & Psychiat.* **42**:842-861 (Nov.) 1939.

5. Löwenburg and Waggoner.⁴ Beck, D. J. K., and Russell, D. S.: Oligodendrogliomatosis of the Cerebrospinal Pathway, *Brain* **65**:352-372, 1942. Blumenfeld, C. M., and Gardner, W. J.: Disseminated Oligodendroglioma, *Arch. Neurol. & Psychiat.* **54**:274-279 (Oct.) 1945.

through the meninges of the cerebrospinal axis. Failure to observe such a tendency could well be due to the few autopsy records available in this series. At operation, in several instances, seeding on the ependyma of the ventricle, at a distance from the main mass of the lesion, was noted.

Bailey and Cushing,² when first reporting on this type of glioma, remarked on the long course of the tumors and gave the postoperative survival as four plus years. Bailey and Bucy,⁶ in 1929, reported that the average postoperative period of survival in a series of 13 cases of oligodendroglioma was 39.2 months, with an average preoperative duration of symptoms of 57.5 months. The ultimate outcomes in series of tumors of the brain observed by Van Wagenen,⁷ Cairns⁸ and Davidoff,⁹ during their services with Dr. Cushing, were reported in 1934, 1936 and 1940, respectively. Data on the small series of cases of oligodendroglioma followed by these observers generally confirmed the favorable prognosis previously noted for this type of glioma. Elvidge, Penfield and Cone^{1b} were the first to note that postoperative survival in cases of oligodendroglioma was disproportionately lower than the preoperative duration. In their series of 8 cases, the preoperative duration of symptoms averaged 11.7 years, with postoperative survival periods of three, three, two and one-half, and one-third years—3 of the patients in their series being still alive four, eleven and sixteen months after operation. They stated the belief that the rate of growth of this type of glioma tends to increase late in its evolution and that operation speeds it up yet more. While this discrepancy between the preoperative and the postoperative duration is not so broad in our series, it is present. The average postoperative period of survival, indeed, was less than two years. The segregation of cases in which the tumor was growing particularly within the ventricular system altered the prognosis only slightly. It did appear that the preoperative duration of symptoms of patients with the ventricular type was shorter than that of patients with the hemispheric type, while there was little difference between the two groups in length of postoperative survival.

In no instance were there sufficient mitoses or other evidences of rapid growth which could be correlated with the clinical course of the patient to justify the formation of a group of cases of the oligoblastomatous type. It was not possible, therefore, from the histologic appearance

6. Bailey, P., and Bucy, P. C.: Oligodendrogliomas of the Brain, *J. Path. & Bact.* **32**:735-751, 1929.

7. Van Wagenen, W. P.: Verified Brain Tumors (End Results of One Hundred and Forty-Nine Cases Eight Years Postoperative), *J. A. M. A.* **102**:1454-1458 (May 5) 1934.

8. Cairns, H.: Ultimate Results of Operations for Intracranial Tumors, *Yale J. Biol. & Med.* **8**:421-492, 1936.

9. Davidoff, L. M.: A Thirteen Year Follow-Up Study of a Series of Cases of Verified Tumors of the Brain, *Arch. Neurol. & Psychiat.* **44**:1246-1261 (Dec.) 1940.

of the tumor, to segregate a group in which the prognosis could be said to be more favorable.

The symptomatology of this type of glioma is interesting, since there was a clear distinction between cases of the ventricular and cases of the hemispheric type. The former were characterized early by the symptoms of increased intracranial pressure. Focal signs and convulsive seizures were generally absent, or appeared late in the course of the disease. Focal convulsive seizures were common in cases of the hemispheric type, and often were the first manifestation of the disease. Penfield and Erickson¹⁰ noted that the two factors which influence the relationship between brain tumor and epileptic seizures are the distance which separates the tumor from the sensorimotor cortex and the rapidity of growth of the tumor. The ventricular tumors are deep-lying lesions and make themselves manifest relatively quickly. The hemispheric lesions, usually superficial and generally located in the frontal lobes, are thus frequently associated with epileptic seizures.

SUMMARY

Six of the present series of 25 oligodendrogliomas (24 per cent) were located principally within a lateral and/or the third ventricle. Seventeen of the 19 oligodendrogliomas growing in the parenchyma of the brain were located in one or the other, or in both frontal lobes.

Patients with ventricular tumors had a short preoperative course (average of seven and one-half months), and the symptoms were those of increased intracranial pressure. Patients with hemispheric tumors had a longer preoperative duration of symptoms (average, thirty-five months), and the history generally was one of focal symptoms, often jacksonian seizures, preceding the symptoms and signs of increased intracranial pressure.

The average period of survival after operation in this series was less than two years. Of the 5 patients with ventricular tumor who survived operation, only 1 is still alive and well (at the end of fifty months). The average period of survival of the remaining 4 patients was twelve and one-half months, with a range of two to twenty-three months. Fifteen patients with hemispheric tumor recovered from operation, but only 4 are still alive, ten to thirty months later. The remaining members of this group survived an average of twenty-two months, with a range varying from five to forty-eight months.

3400 Spruce Street.

10. Penfield, W., and Erickson, T. C.: *Epilepsy and Cerebral Localization*, Springfield, Ill., Charles C Thomas, Publisher, 1941.

SIGNIFICANCE OF CHANGES IN THE ELECTROCARDIOGRAM AFTER ELECTRICALLY INDUCED CONVULSIONS IN MAN

M. D. ALTSCHULE, M.D.

W. M. SULZBACH, M.D.

AND

K. J. TILLOTSON, M.D.

WAVERLEY, MASS.

BELLET and associates¹ studied the effects of electrically induced convulsions on the electrocardiogram in man and recorded the frequent occurrence of sinoauricular block, sinus arrhythmia, shifting pacemaker, auricular premature beats and auriculoventricular nodal rhythm; these arrhythmias were considered to be consequent to vagal hyperactivity. Reference may also be found in the clinical literature to the occurrence of auricular fibrillation after electroshock therapy.² On the other hand, Nyman and Silfverskiöld³ emphasized changes in the P and T waves and laid little emphasis on the development of arrhythmias and bradycardia. In order to evaluate the frequency, degree and significance of cardiac inhibition which might occur as a consequence of electrically induced convulsions, it was considered of interest to make further observations on the electrocardiogram and simultaneously to study the changes in the circulation time.

MATERIAL AND METHODS

Thirty studies were made in 10 patients. The ages of the subjects varied from 17 to 56; 9 were women. Five patients were studied once or twice, and the other 5 were studied four to seven times each.

From the Clinical Services of the McLean Hospital, Belmont; the Medical Research Laboratories of the Beth Israel Hospital, Boston, and the Departments of Psychiatry and Medicine of Harvard Medical School.

1. Bellet, S.; Kershbaum, A., and Furst, W.: The Electrocardiogram During Electric Shock Treatment of Mental Disorders, *Am. J. M. Sc.* **201**:167, 1941.

2. Hayman, M.: The Prophylaxis of Cardiac Complication in Electroshock Therapy, *Am. J. Psychiat.* **102**:316, 1945. Smith, L. H.; Hastings, D. W., and Hughes, J.: Immediate and Follow-Up Results of Electroshock Therapy, *ibid.* **100**:351, 1943.

3. Nyman, E., and Silfverskiöld, B. P.: Kreislaufstörungen bei Krampfanfällen epileptischen Typs: III. Das Elektrokardiogramm beim Elektroschock, *Acta med. Scandinav.* **114**:223, 1943.

Standard three lead electrocardiograms were made before induction of the convulsive seizure. The electrocardiographic electrodes were left in place, and as soon as the convulsion was over another tracing from all three standard leads was begun. The circulation time was studied by the fluorescein method,⁴ measurements being made before and again approximately one minute after the convulsion.

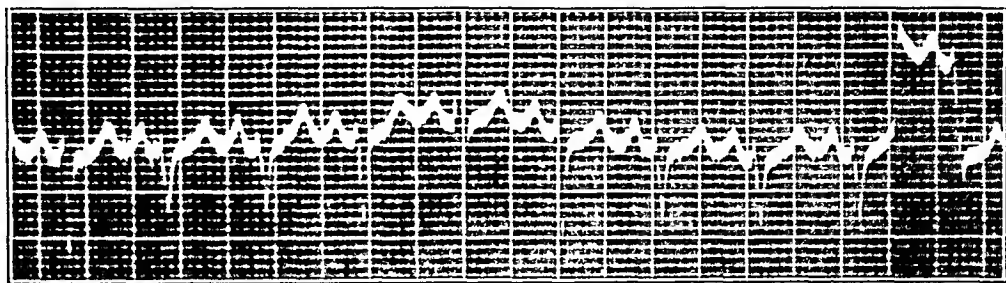


Fig. 1.—Rhythmic variation in QRS complexes with respiration after a convulsion.

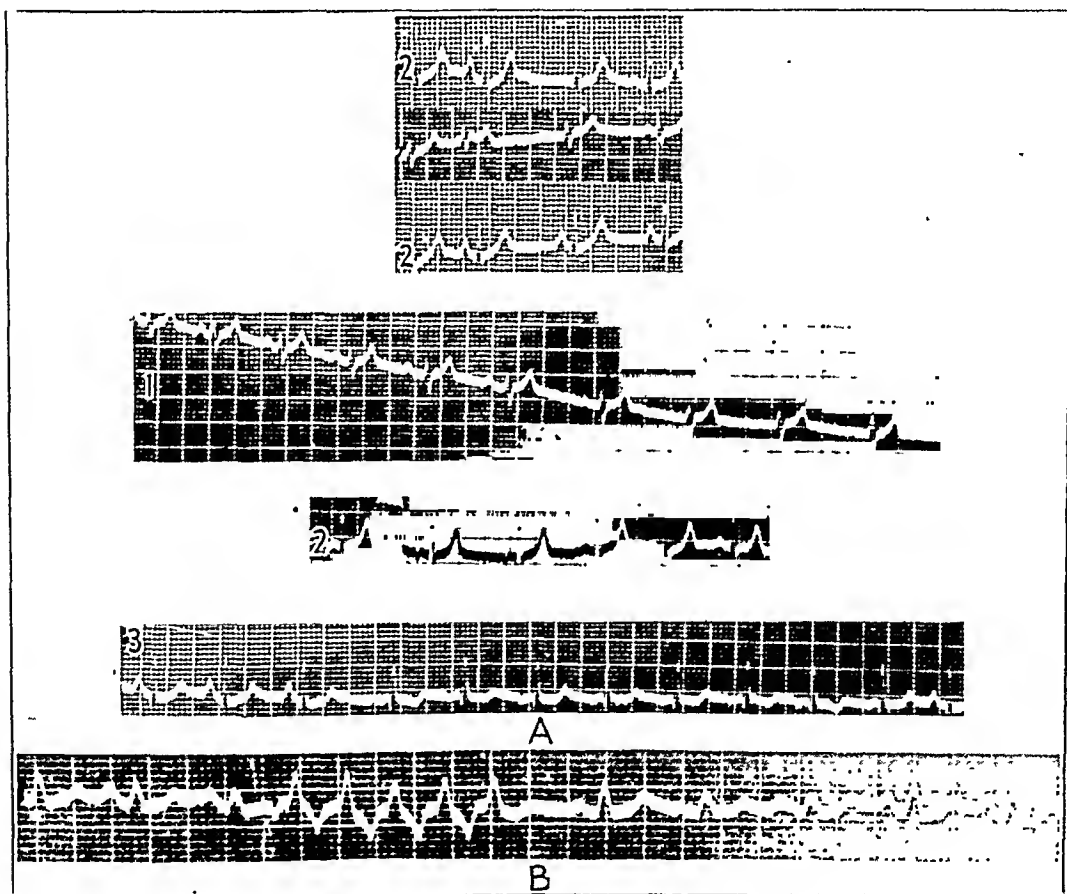


Fig. 2.—*A*, arrhythmias occurring on different occasions in the same patient after convulsion: sinus arrhythmia, auriculoventricular nodal rhythm, auricular premature beats and variations in the P-R interval. *B*, brief paroxysm of auricular tachycardia after convulsion.

4. Fishback, D. B.; Guttman, S. A., and Bramson, E. B.: An Objective Method of Determining Blood Velocity (Fluorescein Method), *Am. J. M. Sc.* 203:535, 1942.

OBSERVATIONS

The average cardiac rate was accelerated in every instance. The increase in rate ranged from 22 to 94 per cent; the lesser increases occurred in patients in whom short but recurrent periods of arrhythmia developed. The ventricular gradient was decreased in 3 patients on whose tracings measurements were made.

Increase in the size of the P wave was a uniform finding at some time after the convulsion except when aberrant auricular or nodal beats occurred. Similarly, every tracing taken after the seizure showed a rhythmic variation in the size and shape of the QRS waves, the varia-

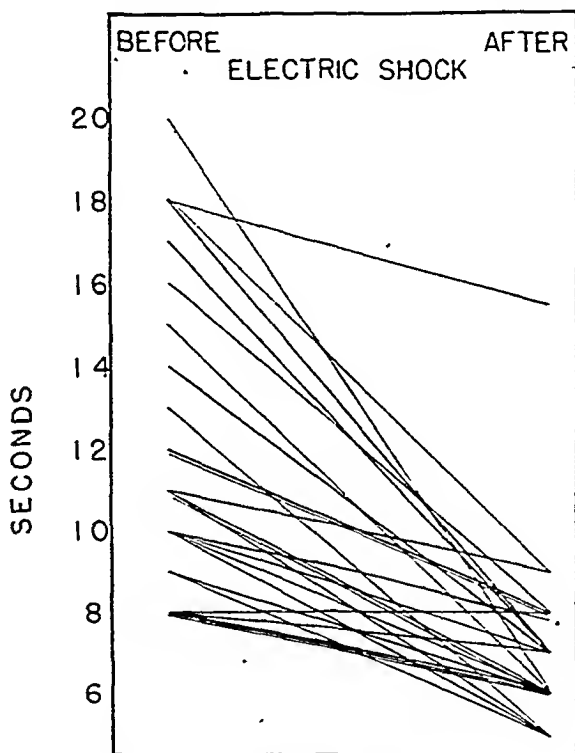


Fig. 3.—Circulation times before and after convulsion.

tion consisting in a change from tall, narrow complexes to short complexes and back again (figs. 1 and 3); the rhythm of this change corresponded with the respirations. Four patients studied a total of thirteen times showed depression of the S-T interval in one or more leads on eleven occasions (fig. 2 *A* and *B*); this was only minimal for 3 of the patients.

Arrhythmias occurred in all but 2 of the 10 patients. The patients who were studied four to seven times each did not necessarily exhibit arrhythmia on each occasion. It was found in all 4 studies on 1 patient, but in 3 others studied four or more times each it was found in only one-half the studies on each. The arrhythmias found most often were

a shifting pacemaker, auricular premature beats, pronounced sinus arrhythmia, periodic bradycardia and nodal rhythm (fig. 2 *A*); in addition, auricular tachycardia occurred in 1 instance (fig. 2 *B*). The arrhythmias changed from one type to another rapidly (fig. 2 *A* and *B*). One patient in whom a cardiac arrhythmia developed after the electrically induced convulsion exhibited occasional ventricular premature beats.

Studies of the circulation time showed acceleration of the blood flow after the convulsive seizure in every case (fig. 3).

COMMENT

The present study corroborates the previously recorded occurrence¹ after electrically induced convulsions of shifting of the site of origin of the heart beat, as evidenced by pronounced sinus arrhythmia, periods of sinus bradycardia, frequent auricular and nodal premature beats and, in 1 instance, auricular tachycardia. This type of disturbance in cardiac rhythm is a consequence of vagal hyperactivity; the results of a few studies by Bellet and associates¹ in which atropine minimized these changes are in accord with this concept. Similarly, the development of auricular fibrillation² after electroshock therapy is to be interpreted as a manifestation of increased vagal tone.⁵ The occurrence of vagal arrhythmia goes with other evidences of autonomic stimulation exhibited by patients during and after convulsive seizures. It is not clear, however, whether the increase in vagal tone in the heart is the result of stimuli from the brain, of reflexes activated by the cardiorespiratory changes induced by the 'convulsion'⁶ or of the potentiation of acetylcholine action by the acidosis which occurs^{6a} as a result of high carbon dioxide levels. Similarly, the part played by asphyxia^{6a} in the genesis of the vagal stimulation observed cannot be evaluated. However, irrespective of the mechanism of production of increased vagal tone during electrically induced convulsions, it is probable that the acidosis which occurs^{6a} as the result of accumulation of carbon dioxide increases the action of whatever acetylcholine is liberated by inhibiting cholinesterase and thereby potentiating the vagal inhibition of the heart.⁷ The vagal hyperactivity noted does not give rise to sufficient cardiac inhibition

5. Altschule, M. D.: Relation Between Vagal Activity and Auricular Fibrillation in Various Clinical Conditions, *New England J. Med.* **233**:265, 1945.

6. (a) Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Effects of Electrically Induced Convulsions upon Respiration in Man, *Am. J. Psychiat* **103**:680, 1947. (b) Silfverskiöld, B. P., and Åmark, C.: Disturbance of Circulation in Convulsions of the Epileptic Type: II. Arterial and Venous Pressures During Electroshock, *Acta med. Scandinav.* **113**:191, 1943. (c) Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Effect of Electrically Induced Convulsions on Peripheral Venous Pressure in Man, *Arch. Neurol. & Psychiat.* **58**:193 (Aug.) 1947.

7. Gesell, R.; Mason, A., and Brassfield, C. E.: Acid Humoral Control of Heart Beat, *Am. J. Physiol.* **141**:312, 1944.

to slow the systemic circulation and is therefore not a factor in the increase in venous pressure which occurs during electrically induced convulsions.⁸ It appears that the occurrence of this type of arrhythmia usually gives rise to no hazard in patients without antecedent cardiac disease. It is to be noted that arrhythmias of vagal origin may also occur after seizures induced with convulsant drugs.⁹

The increase in the size of the P wave which occurred during the immediate postconvulsive period is of some interest in that it probably is an indication of dilatation of the auricle, consequent here to increased venous pressure and venous return. Earlier studies⁸ revealed the development of high venous pressure levels during electrically induced seizures and evidence of increased venous return immediately after the seizure. It is of interest that a similar increase in size of the P wave has been noted in patients receiving large infusions intravenously,¹⁰ and after the Valsalva procedure,¹¹ and is also well known to occur with auricular dilatation consequent to mitral stenosis.

Changes in the ventricular complexes caused by convulsions are not important. The rhythmic variation in the shape of the QRS complex observed in all cases is probably respiratory in origin; respiration for several minutes after the seizure is markedly hyperpneic^{6a} and shifts in the level of the diaphragm must be extreme. The variable changes in the T waves and the inconstant depression of the S-T interval noted were not significant, for they were not associated with changes in the direction of the ventricular gradient.

SUMMARY

The electrocardiogram after electrically induced convulsive seizures often shows evidence of a considerable increase in tone of the vagus innervation of the heart. The increase in vagal activity usually does not induce sufficient cardiac inhibition to cause more than transitory bradycardia; the systemic circulation is not slowed. Other electrocardiographic changes associated with variations in respiration and circulation after electroshock therapy are also noted.

McLean Hospital.

8. Silfverskiöld and Åmark.^{6b} Altschule, Sulzbach and Tillotson.^{6c}

9. Dick, A., and MacAdam, W.: Cardiac Complications in Cardiazol Treatment: Observations in Four Cases, *J. Ment. Sc.* **84**:677, 1938.

10. Altschule, M. D., and Gilligan, D. R.: Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: II. The Dynamics of the Circulation, *J. Clin. Investigation* **17**:401, 1938.

11. Liedholm, K.: Studien über das Verhalten des Venendrucks beim Valsalvaschen Versuch, *Acta med. Scandinav.*, 1939, supp. 106.

SPATIAL ORGANIZATION OF VISUAL PERCEPTION FOLLOWING INJURY TO THE BRAIN

M. B. BENDER, M.D.*

AND

H. L. TEUBER, Ph.D.*
NEW YORK

IN A SYSTEMATIC study of patients who had sustained battle injuries of the parieto-occipital lobes,¹ we found 12 with spatial disorientation. The disorders ranged in severity from almost complete "space blindness" to conditions in which the defect seemed confined to homonymous halves, quadrants or even sectors of the fields of vision. Particularly the patients with sector defects presented highly consistent symptoms. However, none of the findings could readily be explained in terms of current theories of visual space perception. Before embarking on an analysis of our case material, we shall, therefore, trace some of the previous attempts at a neurologic and psychologic interpretation of disorders in the visual perception of spatial relations.

Prior to World War I, a disorder in the perception of spatial relations was considered part of a generalized disturbance in intellectual function. Loss of orientation in space as well as the inability to localize objects in space were thus described as more or less incidental symptoms in cases of post-traumatic confusional states and of severe visual agnosias.² Moreover, the clinician's description of the symptoms was

* Now released to inactive duty in the United States Naval Reserve. The observations were made while the authors were on active duty at the United States Naval Hospital, San Diego, Calif.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as official or reflecting the policies of the Navy Department.

1. (a) Bender, M. B., and Teuber, H. L.: Fluctuation, Extinction and Completion in Visual Perception, *Arch. Neurol. & Psychiat.* **55**:627 (June) 1946; (b) Ring Scotoma and Tubular Fields: Their Significance in Head Injury, *ibid.* **56**:300 (Sept.) 1946.

2. (a) Jackson, J. H.: Case of Cerebral Tumour Without Optic Neuritis and With Left Hemiplegia and Imperception, *Roy. London Ophth. Hosp. Rep.* **8**:434, 1876. (b) Hartmann, F.: *Die Orientierung*, Leipzig, F. C. W. Vogel, 1902. (c) Balint, R.: Seelenlähmung des Schauens, optische Ataxie, räumliche Störung der Aufmerksamkeit, *Monatschr. f. Psychiat. u. Neurol.* **25**:51, 1909. (d) von Stauffenberg, W.: Ueber Seelenblindheit: Nebst Bemerkungen zur Anatomie der Sehstrahlung, *Arb. a. d. hirnanat. Inst. Zürich* **8**:1, 1914.

often vitiated by an uncritical acceptance of the available psychologic theories of space perception.

Von Stauffenberg's approach^{2a} may be considered characteristic of this attitude. A "visuospatial agnosia" was assumed to involve a peculiar difficulty in the invoking of "visuomotor engrams." The latter, in turn, was thought to be due to the fact that the patient's momentary visual impressions had become too indistinct to allow him to elaborate or mobilize the requisite "spatial signs." Such an analysis implicitly accepted a host of psychologic concepts and theories (e. g., "engrams," "mnemic dispositions") which were current at the time, before the first world war.³ On the whole, the problem was not critically attacked until pathologic material became abundant. During and after the first world war there were many cases of changes in perceptual functions as the result of gunshot wounds of the brain. Among these were the classic instances of disorders in the visual perception of space—the cases described by Holmes,⁴ Riddoch,⁵ Goldstein and Gelb,⁶ Fuchs,⁷ Poppelreuter,⁸ Best,⁹ Piéron¹⁰ and many others. (For summaries of these cases, see Kleist¹¹ and Klüver.¹²)

3. It is noteworthy that, as late as 1941, W. R. Brain (Visual Object-Agnosia with Special Reference to the Gestalt Theory, *Brain* **64**:63, 1941) analyzed a case of "mind-blindness" basically in the same terms as did von Stauffenberg,^{2a} in 1914.

4. Holmes, G.: (a) Disturbances of Visual Orientation, *Brit. J. Ophth.* **2**: 449 and 506, 1918; (b) Disturbances of Visual Space Perception, *Brit. M. J.* **2**: 230, 1919.

5. Riddoch, G.: Dissociation of Visual Perception Due to Occipital Injuries, with Especial Reference to Appreciation of Movement, *Brain* **40**:15, 1917.

6. (a) Goldstein, K., and Gelb, A.: Zur Psychologie des optischen Wahrnehmungs und Erkennungsvorgangs, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **41**:1, 1918. (b) Gelb, A., and Goldstein, K.: Psychologische Analysen hirnpathologischer Fälle auf Grund von Untersuchungen Hirnverletzer, Leipzig, Johann Ambrosius Barth, 1920. (c) Gelb, A.: Die psychologische Bedeutung pathologischer Störungen der Raumwahrnehmung, *Ber. ü. d. Kong. f. exper. Psychol.* **9**:22, 1926.

7. Fuchs, W.: Untersuchungen über das Sehen der Hémianopiker und der Hemiamblyopiker, *Ztschr. f. Psychol.* **86**:1, 1921.

8. (a) Poppelreuter, W.: Die psychischen Schädigungen durch Kopfschuss im Kriege 1914-1916: I. Die Störungen der niederen und höheren Sehleistungen durch Verletzungen des Okzipitalhirns, Leipzig, Leopold Voss, 1917, vol. 1; (b) Zur Psychologie und Pathologie der optischen Wahrnehmung, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **83**:26, 1923.

9. Best, F.: (a) Hemianopsie und Seelenblindheit bei Hirnverletzungen, *Arch. f. Ophth.* **93**:49, 1917; (b) Ueber Störungen der optischen Lokalisation bei Verletzungen und Herderkrankungen im Hinterhauptlappen, *Neurol. Centralbl.* **38**:427, 1919.

10. Piéron, H.: (a) Des degrés de l'hémianopsie corticale: l'hémiastéréopsie, *Compt. rend. Soc. de biol.* **74**:1955, 1916; (b) Thought and the Brain, New York, Harcourt Brace & Company, 1927.

The most obvious result of the work of these investigators was an increase in factual knowledge. Thus, some observers, such as Riddoch,⁵ noted that certain forms of spatial disorientation could be limited to the visual sphere, and even to homonymous half-fields. Yet in the interpretation of their findings the majority of the authors, as represented by Holmes,⁴ Riddoch,⁵ Piéron^{10a} and Best,^{9b} continued to use the conceptual tools of the traditional theory of space perception.

These traditional theories of space perception, which still loom so large in neurologic terminology, are basically associationistic, although the "mental elements" of the older associationistic doctrines may have been cast into the form of reflexes and quasireflexes of the neopavlovian school.¹³ The general assumption of these theories is as follows: Tridimensional organization of perception is always a complex process, based on the secondary integration, in "higher" cortical centers, of originally bidimensional and unnoticed sensations (the "cues" of distance and depth).

Localization in the bidimensional (coronal) plane itself is assumed to be based on a simple direction factor, viz., the specific "local sign" of each retinal point.¹⁴ Tridimensional space, according to the same traditional theories, is achieved by the organism on the basis of even more complex processes of integration and interpretation of sensory data. Stereoscopic vision is thus "elaborated" from the famous cues of depth.¹⁵

11. Kleist, K.: *Kriegsverletzungen des Gehirns*, in *Handbuch der ärztlichen Erfahrungen im Weltkriege*, Leipzig, Johann Ambrosius Barth, 1922, vol. 4, p. 343.

12. Klüver, H.: *Visual Disturbances After Cerebral Lesions*, *Psychol. Bull.* **24**:316 and 358, 1927.

13. Lashley, K. S., and Wade, M.: *The Pavlovian Theory of Generalization*, *Psychol. Rev.* **53**:72, 1946.

14. On the basis of a concept of Lotze (*Medicinische Psychologie, oder Physiologie der Seele*, Leipzig, Weidmann, 1852), who formulated it in a somewhat different connection, local signs are considered to determine the above and the below, the right and the left, in the visual field with relation to the anatomic fovea.

15. These cues are usually classified as uniocular and binocular. Considerable effort has been spent in study of the former, since it has always been known that monocular subjects may possess excellent depth perception. Under normal conditions, however, the most essential determinant for any accurate perception of depth and distance is assumed to be furnished by binocular vision, or the so-called binocular parallax. This is the stereoscopic effect of the fusion of the slightly dissimilar images obtained by the two eyes. The traditional views on depth perception are well developed in Carr's monographic presentation (Carr, H.: *An Introduction to Space Perception*, New York, Longmans, Green & Company, 1935). Brief orientations were given by Woodworth⁴⁰ (pp. 651-683) and by Duke-Elder (Duke-Elder, W. S.: *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, vol. 1, pp. 1038-1058 ["Binocular Perceptions"] and 1059-1081 ["Perception of Space"]). For a historical orientation, see Boring (Boring, E. G.: *Sensation and Perception in the History of Experimental Psychology*, New York, D. Appleton-Century Company, Inc., 1942, pp. xv and 644).

Under the influence of these assumptions concerning normal space perception, not only the analysis, but even purely clinical descriptions, of the pathologic material tended to become biased. Neurologists endeavored to identify the particular monocular or binocular "cues" that had become unavailable for the patient. Single factors, such as spasms of accommodation and disorders in oculomotor reflexes (Piéron^{10a}), were suggested as "causes" of the subjective distortions of visual space. The possibility of a total loss of stereoscopic vision was quite seriously considered (Holmes^{4b}). As in the numerous studies on aphasia, the organism was expected to lose its various functional capacities in accordance with the subdivisions of the textbooks.

However, before the end of the first world war, a new trend of research was inaugurated by Kurt Goldstein and his collaborator Adhémar Gelb.⁶ They introduced the concepts of the gestalt theory, which was just then emerging from the psychologic laboratories.¹⁶ However, they did not simply exchange one set of psychologic predilections for another. By challenging the traditional theories, they reopened the entire question of the physiologic basis of space perception. They insisted on a strictly empiric description of the behavioral changes in patients with cerebral lesions. By means of their analyses they developed two principal themes: 1. They described a general syndrome of altered space perception, characterized by "loss of abstract spatial relations." Patients with such a disturbance showed changes in more than one sensory sphere. However, they were not necessarily completely disoriented, since they could often fall back on a concrete motor sequence^{6a} which enabled them to deal fairly efficiently with the spatial aspects of their surroundings. 2. They emphasized the influence of postural tone on perceptual organization, and vice versa.¹⁷

16. The work of the principal representatives of the gestalt "school" (Wertheimer, Köhler, Koffka, Goldstein and Gelb) has been excellently summarized by Hartmann (Hartmann, G. W.: *Gestalt Psychology: A Survey of Facts and Principles*, New York, Ronald Press Company, 1935, p. 325). Ellis (Ellis, W. D.: *A Source Book of Gestalt Psychology*, New York, Harcourt Brace & Company, Inc., 1938) translated abstracts of some of the German publications on the gestalt theory. According to the German writers, the gestalt concept can be described as "any configuration which in its total organization contains more functional properties than the sum of its apparent component parts." With regard to perception, the gestalt theory stresses that organisms react not to discrete stimuli but to total situations. The total situation includes not only the stimulus configuration but also an intrinsically organized pattern of reaction on the part of the responding organisms.²³

17. (a) Goldstein, K., and Riese, W.: *Ueber induzierte Veränderungen des Tonus*, *Klin. Wchnschr.* **2**:1201, 1923. (b) Goldstein, K., and Jablonski, W.: *Ueber den Einfluss des Tonus auf Refraktion und Sehleistungen*, *Arch. f. Ophth.* **130**: 395, 1933. (c) A recent review of some of the relevant experimental data has been made by H. Werner (*Motion and Motion Perception: A Study on Vicarious Functioning*, *J. Psychol.* **19**:317, 1945).

This second point, however (the observations on a "tonic substrate of perception"), was somewhat lost sight of in the vigorous debates which followed their original publications. The focus of attention was on the total or partial loss of the patient's ability to manipulate abstract spatial relations. For a while, the clinical phenomena figured prominently in the discussions between the proponents of the older theories of perception and those of the emergent gestalt school. It was then fully recognized that the pathologic material offered clues to an understanding of the physiologic basis of visual perception—both normal and abnormal.

One of the primary concerns of the gestalt group in their opposition to the traditional theory was an effort to overcome the distinction of "simple" and "complex" processes in perceptual functioning. Tridimensional visual space, they asserted, is inherent in all processes of visual perception. The classic "cues" of depth and distance were admitted to be necessary conditions for an accurate judgment of depth and distance, but in themselves they were not considered sufficient to make depth perception possible.¹⁸

According to the gestalt theory, depth, distance and shape of visual percepts are conceived as determined by the distribution of forces within a hypothetic "field of forces." The visual field at any moment is organized into "figures" (*Gestalten*) on a "ground" (background). These figures are held together (and "in place," relative to the background) by intrinsic forces, which are assumed to be in stable equilibrium for "strong," or "good," *Gestalten* (such as a circle, seen in the coronal plane), and in unstable equilibrium for "weak," or irregular and ill defined, *Gestalten* (such as any asymmetric figure tilted out of the coronal plane). The assumption of these figure forces is an inference based on a variety of perceptual phenomena. Among these is the

18. In experiments with normal subjects and with subjects with injuries of the brain, the gestalt psychologists endeavored to show that the various "cues" are active only so far as they enter into the total stimulus situation. Thus, they investigated the formation of pseudofoveas in hemianoptic patients in order to demonstrate that the retinal "local signs" must be functional, and cannot be based on structural, point for point relationships. In effect, they added certain factors in depth perception which had received little, or no, attention in the classic doctrine. They emphasized the inherent depth effects of certain colors which may become enhanced after cerebral trauma (Gelb, A., and Goldstein, K.: *Ueber den Wegfall von "Oberflächenfarben," Ztschr. f. Psychol.* **84**:193, 1920), and they added the factor of a binocular time parallax to supplement the long-recognized role of spatial binocular disparity in the depth localization of objects which move rapidly past the eyes (Klemm, O.: *Die binokulare Zeitparallaxe, Neue Psychol. Stud.* **6**: 357, 1932). H. Werner (*Dynamics in Binocular Depth Perception, Psychol. Monogr.* **49**:1, 1937) has begun to develop a unitary theory of monocular and binocular depth perception in which the physiologic processes underlying the stereoscopic effect are brought into close relation with so-called stroboscopic effects.

tendency toward "closure"; a good *Gestalt*, e. g. a circle, is readily seen as complete and closed, even though it may have a gap.¹⁹

Such hypothetic field forces or "vectors," have shown their heuristic value in the consideration of specific problems of normal perception. They were found to be useful conceptual tools in analyzing the apparent distortion of lines (in the so-called optical illusions²⁰) and in predicting the path of apparent movement.²¹

In all these instances, the "vectors" are derived from an analysis of the stimulus distribution within the visual field (e. g., in the instance of optical illusions, the particular line patterns which surround the apparently distorted test figure). However, the implicit assumption is that the visual apparatus, notably the striate cortex itself, reacts as a "field" to photic stimulation. Köhler, in particular, endeavored to demonstrate the existence of such a "cortical field," in which the inferred vectors are represented by actual changes in the electrotonus during and after the acts of perception (Köhler and Wallach²²). The hypothesis undoubtedly helps to clarify a number of obscure phenomena of normal vision.

On the other hand, the introduction of these concepts of fields of force has been justly criticized because they involve a number of *ad hoc* assumptions (Goldstein²³) and because they are exceedingly difficult to cast into concrete neural terms.²⁴ Evidently, the older associationistic or quasiassociationistic theories have the advantage of agreeing well with the predominant conception of the central nervous system as an aggregate of synaptic junctions.

19. Thus, as Koffka (Koffka, K.: *Some Problems of Space Perception*, in Murchison, C.: *Psychologies of 1930*, Worcester, Mass., Clark University Press, 1931) has pointed out, a perspective drawing of a cube will be seen in three dimensions, not because of any binocular cues (it can be viewed monocularly, and still gives the impression of depth), or because of experience (or assimilation with stored images of cubes), since actual cubes look very different indeed from a schematic perspective drawing. Koffka's explanation is, rather, that the line pattern becomes a "better" (more equilibrated, more symmetric) figure if seen in three dimensions than it could be if seen as a two dimensional configuration. There are inherent "stresses" for depth in such a figure which determine its relative orientation in space; and these stresses are in no way different from the forces which lead to the organization of figures in the bidimensional plane.

20. Orbison, W. D.: *Shape as a Function of the Vector-Field*, *Am. J. Psychol.* **52**:31, 1939.

21. Brown, J. F., and Voth, A. C.: *The Path of Seen Movement as a Function of the Vector-Field*, *Am. J. Psychol.* **49**:543, 1937.

22. Köhler, W., and Wallach, H.: *Figural After-Effects: An Investigation of Visual Processes*, *Proc. Am. Philos. Soc.* **88**:269, 1944.

23. Goldstein, K.: *The Organism*, Evanston, Ill., American Psychological Review, 1939.

24. Lashley.⁶³ It should be noted that both these critics of the specific vector-field terminology are otherwise in agreement with certain main principles of the gestalt theory

It may be for this reason that these more recent developments of the gestalt theory have played no role in the analysis of pathologic material. A further, more obvious reason can be found in the relative scarcity of new cases²⁵ in the period between the two world wars. Except for the continued research of such investigators as Goldstein and Jablonski^{17b} and von Weizsäcker,²⁶ interest in the description of disorders in the visual perception of space lagged until recently, when new material appeared among the casualties of the second world war.²⁷ Brain,²⁸ in presenting such new cases, reviewed some of the earlier contributions to the subject and gave the first inclusive clinical classification of disorders in the organization of visual space. In his interpretations of these disorders, however, he limited himself to a brief reference to the traditional theories of space perception.

In our own study of battle casualties of World War II, we therefore endeavored to test in some detail the applicability of a field theory to specific forms of spatial disorientation resulting from cerebral trauma. In the following reports, we shall consider 2 of the 12 cases which were characterized by a specific disability to localize objects in a limited portion of the field of vision. These cases were chosen because their syndromes were somewhat complementary.

In the analysis of the disorders in these cases by means of special tests, major emphasis was placed on the modifications in perceptual functions (positive symptoms) rather than on a mere demonstration of any specific deficiency or loss.²⁹ Specifically, we examined for the following factors: 1. Residual visual function: (a) form discrimination; (b) color perception; (c) after-imagery; (d) tachistoscopic efficiency;

25. (a) Halpern, F.: Kasuistischer Beitrag zur Frage des Verkehrtsehens, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **126**:246, 1930. (b) Laubenthal, F.: Zur Pathologie des Raumerlebens, unter besonderer Berücksichtigung des Sehraums, *ibid.* **162**:202, 1938. (c) Scheller, H., and Seidemann, H.: Zur Frage der optisch-räumlichen Agnosie, *Monatschr. f. Psychiat. u. Neurol.* **81**:97, 1931. (d) Riddoch, G.: Visual Disorientation in Homonymous Half Fields, *Brain* **58**:376, 1935. (e) Kanzer, M., and Bender, M. B.: Spatial Disorientation with Homonymous Defects of the Visual Field, *Arch. Ophth.* **21**:439 (March) 1939.

26. von Weizsäcker, V.: Ueber eine systematische Raumsinnstörung (Der Fall H. B.), *Deutsche Ztschr. f. Nervenhe.* **84**:179, 1925.

27. Paterson, A., and Zangwill, O. L.: Disorders of Visual Space Perception Associated with Lesions of the Right Cerebral Hemisphere, *Deutsche Ztschr. f. Nervenhe.* **67**:331, 1944.

28. Brain, W. R.: Visual Disorientation with Special Reference to Lesions of the Right Cerebral Hemisphere, *Brain* **64**:244, 1941.

29. (a) Jackson, J. H.: On the Evolution and Dissolution of the Nervous System, *Lancet* **1**:555, 649 and 739, 1884. (b) Head, H.: Aphasia and Kindred Disorders of Speech, New York, The Macmillan Company, 1926, vol. 1, pp. xvi and 550; vol. 2, pp. xxxiv and 430. (c) Goldstein, K.: After Effects of Brain Injuries in War, New York, Grune & Stratton, Inc., 1942. (d) Klüver, H.: Functional Significance of the Geniculo-Striate System, *Biol. Symposia* **7**:253, 1942.

(*e*) fusion of visual flicker; (*f*) ability to obtain stroboscopic effects, and (*g*) phenomenal speed of a stimulus moving at standard speed.

2. Visual perception of spatial relations. This was evaluated by means of (*a*) pointing tests; (*b*) bisection of lines; (*c*) standard tests of monocular and binocular perception of depth, including the three string experiment, tests of fusion ability and stereoscopic tests and (*d*) tests for perception of shape and size at varying distances.

3. Intellectual functions pertinent to generalized orientation in space, as manifested in (*a*) map making, (*b*) route finding, (*c*) drawing and copying, (*d*) grouping and sorting of objects and (*e*) body scheme function.

General examination included neuropsychiatric evaluation and psychometric and Rorschach studies.

REPORT OF ILLUSTRATIVE CASES

CASE 1.—A 22 year old lieutenant in the United States Marine Corps was caught in a burst of shrapnel during the invasion of Saipan on June 15, 1944. He was hit simultaneously on the right side of his head, on the left hand and in the axilla. As soon as he was struck, he had a sensation of being "clubbed." There was sharp pain on the right side of his head, and he had the impression of being blinded. He staggered around with eyes closed, heard the men of his company calling for him, fell down on his knees and lost consciousness when he struggled to rise.

Three days later, when he thought he regained consciousness, he saw a chaplain standing on his right and a medical officer on his left. At this time he was tormented by a peculiar sensation that the entire left side of his body "just wasn't there." During the following days this impression predominated, but it was sometimes replaced by an intense feeling of numbness and coolness over the left side of the body. At other times the left side was oversensitive. By looking at the extremities on his left, he could satisfy himself that he was able to move them. However, he was never aware of any active or passive motion on that side, except by using his visual sense. There were no illusory feelings of motion. The gross sensory disturbances, especially the impression of absence of the entire left side, persisted after an operation, which was performed on July 31, 1944. At that time, there was a granulating wound with slight drainage within a defect in the right parietal area of the skull. Roentgenographic studies revealed numerous tiny fragments of bone embedded in the brain substance within an area of laceration in the right motor cortex (fig. 1). The destruction extended posteriorly into the sensory area (fig. 1).

At operation, twenty-two fragments of bone, varying in depth from $\frac{1}{2}$ to $2\frac{1}{2}$ inches (1.5 to 6.5 cm.) beneath the outer surface of the brain, were removed. A small abscess lying deep against the wall of the lateral ventricle was evacuated. After this operation, the patient showed left hemiplegia, weakness of the left side of the face and loss of kinesthesia and complete astereognosis on the left. The hemiplegia improved steadily during the next twelve months. The patient was returned to limited duty and was eventually able to typewrite, swim and run, and even qualified as a marksman. Off duty, he piloted a private plane.

This remarkable compensation of his defects contrasted strangely with the objective neurologic findings, as established on Nov. 1, 1945, when he was first

seen by us. There was hemiparesis of the left side of his body, with all the classic signs of involvement of the pyramidal tract. The muscles of the left leg were atrophic. The hand and foot were cooler on the left side than those on the right and often dripped with perspiration.

Except for point localization and vibration sense, which were only slightly impaired on the left side, there were definite sensory changes, all limited to the left half of the body. Thus, pain, touch and temperature sensibility showed a defect of the cortical type. Ability to appreciate the position of the limbs (whether actively or passively assumed) was lost in the patient's toes, fingers, ankle, wrist, elbow and knee on the left side. With this, there were pronounced incoordination and pseudo-athetoid movements on the left. There was complete astereognosis on the left side, including the left side of the lips. Graphesthesia was lost in the distal half of the upper and lower extremities on the same side. Below the mid thigh and over the entire left upper extremity, the patient was unable to judge the directions of lines drawn on his skin. Ability to discriminate two points applied simultaneously was



Fig. 1.—Roentgenogram of the skull, revealing a bony defect in the right parietal region.

much impaired below the level of the mid thigh and over the entire upper extremity on the left side.

Repeated special tests of tactile sensibility showed that with simultaneous stimulation of corresponding points on the right and the left side of the body, there was immediate and complete "extinction" of sensations on the left. This was found even for stimulations produced by scratching with sharp objects and by application of vibrating tuning forks. Moreover, the sensory adaptation time was found to be much decreased for all sensations, including kinesthesia, on the implicated side. This was most pronounced in the acral regions. When the patient held his upper extremities outstretched and his eyes were closed, he soon lost all awareness of the presence of the left fingers and hand.³⁰

Examination of the eyes showed normal fundi. In confrontation tests, the field for each eye appeared to be full. However, as soon as the patient was asked to

30. Bender, M. B.: Changes in Sensory Adaptation Time and After-Sensation with Lesions of Parietal Lobe, *Arch. Neurol. & Psychiat.* **55**:299 (April) 1946.

describe the appearance of objects placed in the homonymous left inferior quadrants, it became evident that definite qualitative changes in visual function had occurred in this region of the field. Functions of the rest of the cranial nerves were normal.

VISUAL SYMPTOMS

Subjective Complaints.—Until special tests were applied to the left lower quadrants of the fields of vision, the patient had only casual and nonspecific visual complaints. The subjective visual symptoms which he reported spontaneously after his injury (and which had remained unchanged to the date of these special examinations) may be described as follows: 1. He experienced increased ocular fatigue when attending the moving pictures. The patient had to shut his eyes several times during the performance to prevent images from becoming blurred or "blacked out" completely. 2. He noted a peculiar tendency for boundaries between colored fields to become indistinct; this he described as a "blurring" of colors. He said he was unable to name colors in the border region of any two adjacent color fields. 3. Blurring and visual fatigue were much more pronounced under conditions of low or artificial illumination. He did not complain of any increase in the discomfort which is normally caused by glare. 4. He was finally aware of an abnormal tendency to rely on central vision alone.

Perimetric and Tangent Screen Studies.—The perimetric fields taken under our standard conditions (distance, 33 cm.; 1 degree white and red targets; illumination, 7 foot candles) revealed no peripheral cuts for form or motion. However, the fields for red showed homonymous indentations on the left, most prominent in the left inferior quadrants (fig. 2). Routine tangent screen examinations revealed no abnormalities. The tangent screen test was then modified to measure the patient's peripheral acuity, as indicated by his ability to resolve a double line in various orientations. These tests were given with targets 2 cm. long at a distance of 150 cm. (large-far constellation) and were repeated with 1 cm. targets at a distance of 75 cm. (small-near constellation). The distance was measured from the patient's eyes to the fixation marks in the center of the tangent screen. The targets were introduced radially from the periphery inward, and the point of greatest eccentricity at which the patient was first able to resolve the test lines in any given meridian was marked off.

Under these conditions, the patient's peripheral acuity was consistently inferior in the left lower quadrant. This inferiority was more pronounced for the large-far constellation than for the small-near constellation. In addition, there was a similar, but milder, contraction for the opposite, or right lower quadrants. This contraction was likewise limited to the large-far constellation. In other words, the patient's functional field, as assessed by his ability to resolve visual patterns, was shrinking with increasing distance, even though the linear dimensions of the test objects were increased in direct proportion to the increasing distance.³¹

Tachistoscopic Examinations.—Results of repeated tachistoscopic tests were consistent with the finding of a relative homonymous defect in the left inferior

31. Bender and Teuber.^{1b} This effect was noted for normal subjects, at least within this range and with such test objects as were employed in our setting. In the psychologic literature the effect is known as the Aubert-Förster phenomenon (Aubert, H.: *Physiologie der Netzhaut*, Breslau, E. Morgenstern, 1865. Jaensch.^{40a} Freeman, E.: *Anomalies of Visual Acuity in Relation to Intensity of Illumination*, *Am. J. Psychol.* 42:287, 1930). However, for our normal control subjects, the effect was less pronounced and the shrinking of the field with increasing distance tended to be symmetric (concentric).

quadrants. With strict monocular fixation (left or right eye) and with his head in a chin rest, pictures, geometric patterns, letters and figures were exposed to the patient's central and paracentral fields. The area of projection extended 8 degrees horizontally from the center of fixation and 6 degrees vertically in either direction. The time of exposure was varied from one to one-fiftieth second, but was usually kept at one-tenth second. At this speed the patient showed a tendency to miss those portions of the slide which were exposed to the left of his median plane. The defect was most pronounced in the lower left quadrants.³²

After-Imagery.—The methods used in testing after-images were the same as those reported in previous communications.³³

From observations on other patients with relative defects in quadrants and half-fields, one would expect a more rapid fading of the after-image in the most involved quadrant. For this patient it was found, instead, that after monocular stimulation with either eye the after-image persisted longest (indeed, abnormally long) in the left lower quadrant. The patient had also great difficulty in obtain-

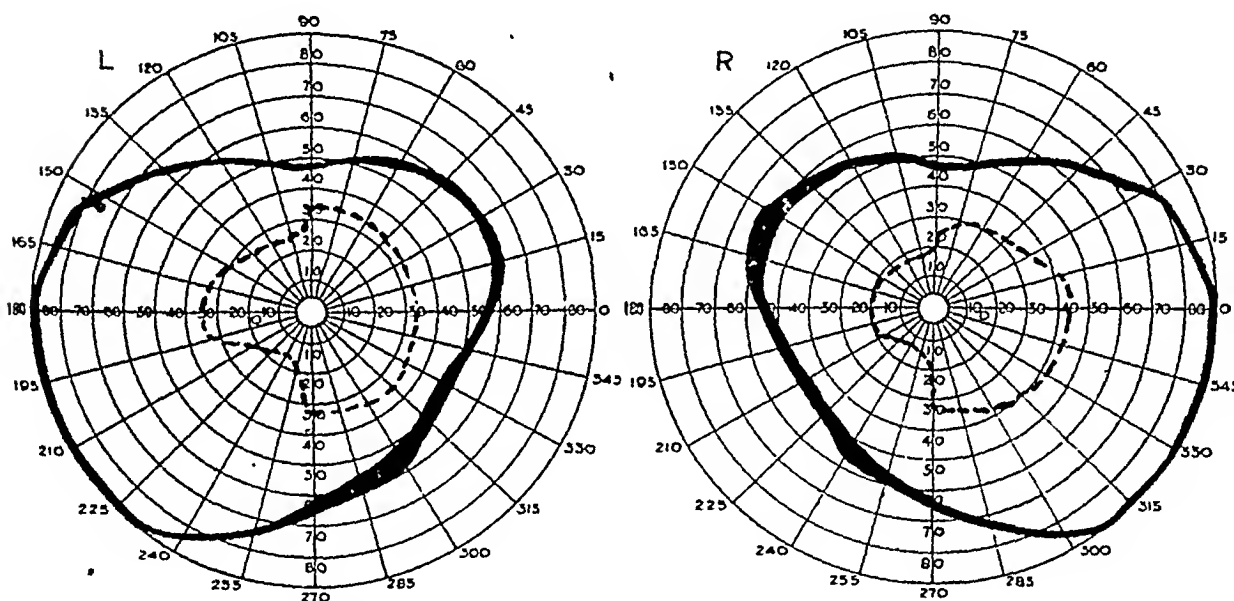


Fig. 2.—Perimetric fields of vision, illustrating homonymous defect for color on the left side. All perimetric tests were performed under an illumination of 7 foot candles, using 10 mm. test objects at a distance of 33 cm. The outer border indicates the extent of the field for perception of movement. The broken lines indicate limits of the field for red.

ing complementary colors in the entire field after monocular stimulation. With binocular exposure, however, the patient's after-images showed the expected rapidly progressing contraction, beginning in the left lower quadrant. Motion after-images (as produced by rotating spirals)^{1b} were readily obtained in any quadrant of both the monocular and the binocular field of vision.

Further Objective Indications of Relative Defect in Left Lower Quadrant.—The results of the tachistoscopic tests were further corroborated by special methods of examination of the fields such as (a) determination of fusion thresholds for

32. The degree of the patient's dark adaptation made no significant difference in the outcome of these tests.

33. Bender, M. B., and Teuber, H. L.: Nystagmoid Movements and Visual Perception, *Arch. Neurol. & Psychiat.* 55:511 (May) 1946; footnote 1 a and b.

visual flicker in different regions of the patient's field; (b) assessment of phenomenal speed, by a matching procedure similar to the one applied by Brown,³⁴ in the central field, as well as in the four quadrants, and (c) measurement of thresholds for stroboscopic motion in different parts of the field. These methods consistently revealed a lowering of physiologic efficiency in the patient's left homonymous fields, especially the inferior quadrants.³⁵

Gross Symptoms of Disorder in Perception in Left Lower Quadrants (Teleopsia and Micropsia).—When similar objects were exhibited to the left and right lower quadrants of the patient's binocular or monocular fields, he reported that the object in the left lower quadrant appeared (1) less brilliant, or somewhat "grayish," or (2) "farther away" than it did when exhibited to the right half of the field at the same objective distance. Usually if tested with the target at 5 to 10 degrees of eccentricity in the left lower quadrant, the patient reported that the image was about half as large as it should be, i.e., as it appeared in the center and the three remaining quadrants of the field. If the target was moved farther toward the periphery of the left lower quadrant, (3) he reported an additional shrinking; *pari passu* with the illusion of decrease in size, the perceived distance of the objects increased. Generally, this tendency toward excessive perceived distance (teleopsia) for objects presented to the patient's left lower quadrant was the most persistent symptom. The teleopsia was accompanied with an illusion of abnormal smallness (micropsia) whenever the object was familiar, that is, when the object's "true" size was known to the patient by experience (fingers, pencils) or by repeated exposure to different quadrants. With unfamiliar objects, such as outline circles or disks, he frequently experienced teleopsia with macropsia. In these instances, the objects, while "dropping back" in space, seemed to him to expand at the same time.

Finally, in addition to the patient's constant tendency to perceive objects in the left lower quadrant as if they were at a great distance (teleopsia), together with the recurrent micropsia and occasional macropsia, there was (4) a tendency to distortion of shapes (dysmorphopsia, metamorphopsia). This distortion took place only at greater eccentricity (beyond 5 degrees from the center of fixation) and was less constant and less pronounced than the previously noted perceptual disturbances.³⁶

The most constant and most pronounced disturbance in the left lower quadrants of the patient's visual fields was (5) an inability to localize objects by pointing. When he was allowed to view a target in direct gaze, his pointing was always correct. Even monocularly, he showed practically no errors, which may have been due to his training as a marksman. Neither was there any gross past pointing with the eyes closed, provided the patient used the normal, or right, hand, once he had ascertained an object's position by touch or by central vision. However, if the

34. Brown, J. F.: The Visual Perception of Velocity, *Psychol. Forsch.* **14**: 183, 1931.

35. Some of the special methods used in this investigation were described in previous communications.¹ As in all other cases, the relative field defect manifested itself in (a) an abnormal increase of phenomenal (perceived) speed, (b) a considerable rise in thresholds for apparent (stroboscopic) motion and (c) a decrease in fusion frequencies for flicker.

36. The pertinent observations on the patient's dysmorphopsia and metamorphopsia will be included in a forthcoming report on disorders in the perception of shape after injury to the brain. (See also Teuber, H. L., and Bender, M. B.: Significance of Changes in Pattern Vision Following Occipital Lobe Injury, *Am. Psychol.* **1**:255 [July] 1946.)

patient was asked to point at a target exhibited in the left lower quadrant a few degrees off his center of fixation, he invariably pointed too far, and at the same time tended to stray to the left, or toward the periphery of the field. This form of past pointing was always more pronounced in the sagittal than in the coronal plane. (Occasionally, he would err by pointing at a roughly corresponding location in the right lower quadrant, thus showing a form of optic allochiria, or transposition of the image into the opposite, or better, region of the field.)

Since the patient's disorientation in visual space seemed highly specific (in the absence of any symptoms of general disorientation in space), and practically limited to the homonymous left lower quadrants, efforts were made to determine more exactly the extent of these difficulties in the visual perception of spatial relations.

Bisection of Lines.—A constant difference in "space values" between the right and the left halves of the patient's fields seemed to be demonstrated by his performance in bisecting lines.³⁷ The patient was instructed to bisect lines presented in different meridians. 1. In the first series of experiments, he was told to fix at a point which he assumed to be in the middle. With binocular and monocular viewing of a horizontal line 152 mm. long, he made constant errors in his attempts at bisection (fig. 3 *A*). It is inferred that the portion located on the defective (left) side must have appeared to him longer than that on the right side. He was not aware of this inequality; all he noted was the fact that the left side appeared farther away and "sloping outward." 2. The patient was then asked to bisect a line with monocular and binocular fixation on one end of the line. The resulting bisections are presented in figure 3 *B*, with the line in the four main orientations. It will be noted that the patient erred practically without exception in "typical"

37. If a normal subject is told to bisect a line oriented in the horizontal meridian, with monocular fixation on its presumed midpoint, he will usually make the temporal portion too long (Kundt's bisection error [Kundt: *Ann. d. Physik.* **120**:118, 1863; cited by Duke-Elder, W. S.: *Textbook of Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, vol. 1]). If, instead, he is told to fix at one end and then to bisect the line, he will tend to make the peripheral portion too long, regardless of in which meridian the line is oriented. The older theories of "space values" and their distribution on the retina (Hering.³⁸ Hillebrand, F.: *Die Stabilität der Raumwerte auf der Netzhaut*, *Ztschr. f. Psychol. u. Physiol. d. Sinnesorg.* **5**:1, 1893. Witasek, S.: *Psychologie der Raumwahrnehmung des Auges*, Heidelberg, C. Winter, 1910. Tschermak, A.: *Augenbewegungen*, in Bethe, A.; Bergmann, G.; Embden, G., and Ellinger, A.: *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1931, vol. 12, pt. 1, pp. 1001-1094) interpreted this tendency as an indication of an unequal distribution of space values on the retina: At the periphery, space values are packed less densely than in central areas of the retina. Hence, a given line, when projected onto the periphery, will appear shorter than it appears in central vision. For this reason, on attempted bisection of the line, the most peripheral portion will be made too long. When a hemianoptic subject is asked to bisect a horizontal line, with fixation on its presumed midpoint, he usually errs in the same direction as a normal subject but to a much greater extent (Liepmann, H., and Kalmus, E.: *Ueber eine Augenmasstörung bei Hemianopikern*, *Berl. klin. Wchnschr.* **37**:838, 1900). Best,³⁹ who subjected to systematic investigation such errors in bisection following injury to the brain, found both "typical" errors and errors in the opposite direction, or "atypical" errors. Fuchs confirmed Best's observations and systematized them in terms of his theory of functional foveas, or pseudofoveas, in defective visual fields.⁷ "Typical" errors were found to be characteristic of cases of hemianopsia; "atypical" errors predominated in cases of hemiambyopia and quadrant amblyopia.

fashion when the line was oriented in the horizontal meridian to the patient's left. A similar error was made when the line lay in the vertical meridian (with the patient fixing on the upper end). That is, in these orientations, the peripheral portion was made too long. Although overestimations of this sort are made by normal subjects, they were evidently excessive in tests on this patient.³⁸

On the contrary, the patient consistently made an "atypical" error (i. e., he made the peripheral portion too short) when the line was oriented to the right of

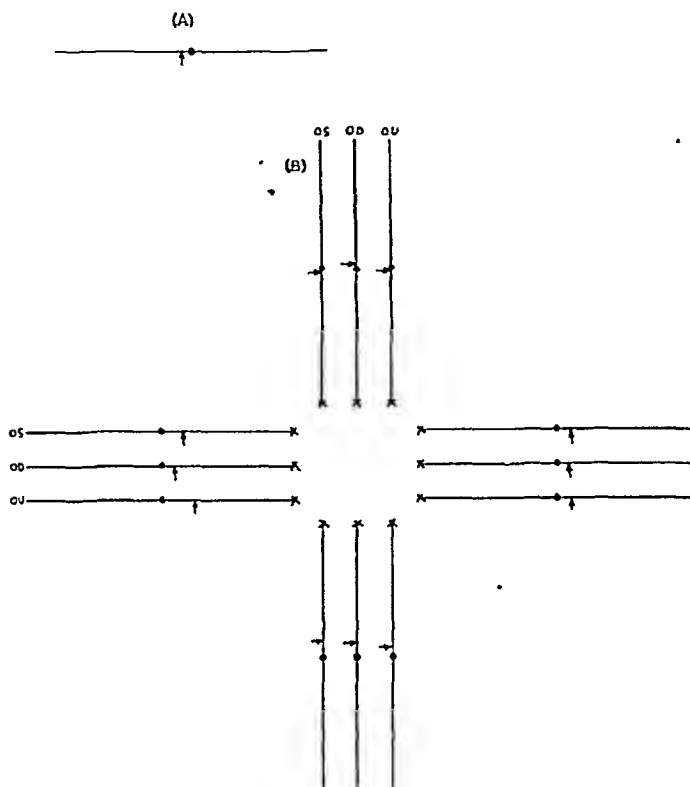


Fig. 3.—Bisection of lines: *A*, result of patient's attempts to bisect a horizontal line (15.2 cm. long) on scanning freely the whole line and fixing on the presumed midpoint. With binocular, as well as with monocular, vision the presumed midpoint was placed too far to the left. *B*, result of patient's attempts to bisect a line, using the right eye (*O.D.*), left eye (*O.S.*), or both eyes (*O.U.*), while fixing strictly at one end of the line (*X*). Each of the lines (which were all 15.2 cm. long) was presented consecutively in the horizontal and vertical meridians (i. e., to the right and the left of the points of fixation, as well as above and below these points). Each test line appeared on a gray cardboard background in the patient's coronal plane, at a distance of 40 cm. from the eyes. The drawing is a composite picture and is intended to reveal the uniformity of the displacement. The dot in the line is the true midpoint. The arrow indicates the place where the patient assumed the midpoint to be.

38. Owing to limitations inherent in the setting, these tests could not be repeated often enough to furnish us with adequate estimates of the patient's variability. Generally, patients err consistently until they become aware of their constant errors. In their attempt to correct the errors, their pointing and bisecting may become much less predictable. The illustrations represent, therefore, only the characteristic behavior on first testing.

his fixation point along the horizontal meridian. In this instance his response was the opposite of that of a normal subject. Apparently to his left, the most peripheral portion seemed to him longer than did the portion in paracentral and central vision.

Three String Experiment.—In studying binocular depth perception in our patients, we used an adaptation of the classic three string experiment. In this setting,³⁹ the subject views three vertical black threads suspended behind an occlusion screen. Behind the threads is a gray background. The three threads are equidistant from each other and are situated in the subject's coronal plane. In the standard experiment, the subject fixes binocularly on the central thread. In successive trials, this thread is presented (a) in the same plane as the other two threads, (b) slightly farther away than the other two and (c) slightly closer than the other two. The subject's task is to judge whether all three threads are actually in one plane or whether they form a concave or convex wedge in relation to his line of regard. In a modification of the classic experiment, the threads are first presented in the coronal plane. The patient is then moved to the right or to the left of the original line of regard. After he has been moved to the side, he is specifically instructed to fix at the middle thread and to indicate how the strings should be readjusted in order to bring all the threads in what he considers his coronal plane.

The two diagrams in figure 4 give characteristic results after the patient was thus moved 15 degrees to the right, and later 15 degrees to the left, of his original central position.⁴⁰ In each instance the results showed that the target (thread) on the left seemed "too far." This teleopsia induced the patient to bring the left thread closer to him, so as to make all three threads appear in what he considered his coronal plane. However, as the diagrams indicate, the distortion in the patient's perception of visual space was not limited to his left side. Under the conditions specified in the experiment, he showed a complementary change in his right field of vision. The thread on the right had to be moved back beyond the true coronal plane (perpendicular to the line of regard in the new position). It will be noted that, regardless of the patient's new position (whether to the right or to the left of the original position), the right thread was moved behind the true coronal plane.

In other words, the patient rearranged the threads within a plane which was at an angle to the true coronal plane. Regardless of the patient's position, the left thread was placed objectively "too close" and the right thread "too far." The patient's behavior thus suggested that his entire subjective coronal plane had rotated around the median, and hence no longer coincided with the "true" coronal plane. Accordingly, whenever the threads were not readjusted to satisfy the patient but were kept, instead, in the "true" coronal plane, the patient experienced them as though rotated through a sizable angle (15 to 30 degrees) around the median. The thread to the patient's left then appeared to him much farther, and the thread to the right much "closer," than they would have appeared to a normal observer.

39. Hering, E.: *Spatial Sense and Movements of the Eye*, translated by C. A. Radde, Baltimore, Williams & Wilkins Company, 1942, pp. xii and 221.

40. (a) Jaensch, E. R.: *Ueber die Wahrnehmung des Raumes*, Leipzig, Johann Ambrosius Barth, 1911, p. 488. (b) Normal observers, on using binocular vision, have little difficulty in arranging the three threads in the coronal plane. Within the range tested, there is usually a slight tendency to make the arrangement concave, but the departures from the true coronal plane rarely exceed 2 to 3 mm. When a normal observer is placed to one side (right or left) of his original line of regard and the strings are kept in their original position, a curious phenomenon is noted. The area defined by the three strings appears to the subject no longer as a plane but as slightly concave. This effect was known to Jaensch, who related it to such phenomena in normal visual perception as the curved appearance of the sky.

An incidental observation during these tests was a certain lability of localization in the sagittal plane. When all three threads had been placed objectively in the coronal plane, the patient reported that the center thread seemed to move back and forth in the sagittal plane. Occasionally, the two outer threads "blackened out." More frequently, only the thread to the left seemed to disappear and reappear at short, irregular intervals. All this occurred even with monocular vision.

In summary, it may be stated that these special tests confirmed the presence of teleopsia, particularly in the left lower quadrants of the fields of vision. This was found on monocular and binocular tests. (a) Teleopsia was the most consistent finding, whereas the concomitant changes in size and shape were not as constant. The latter depended largely on the constellation of the presented objects. (b) The teleopsia itself could be modified in its extent by certain changes in the stimulus pattern. (c) Under certain conditions, the disorders in space, size and shape on the left side sometimes extended to involve the rest of the field. Involvement of the right side of the field was transient and much less pronounced than on the left side.

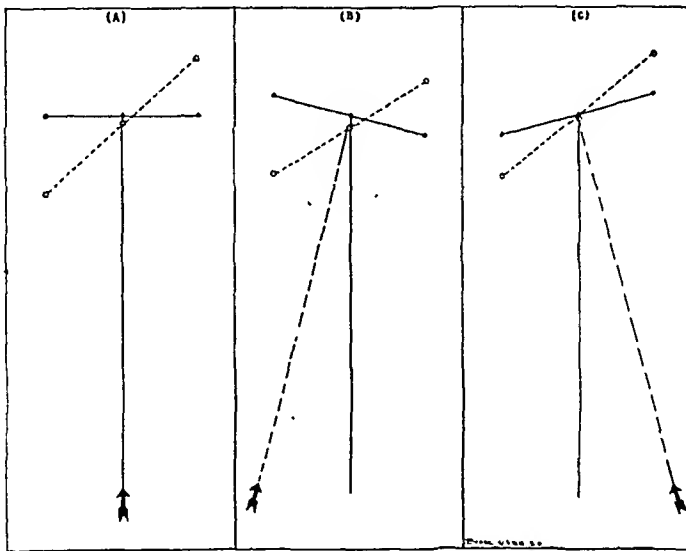


Fig. 4.—Schematic drawing of the patient's attempts to place the three strings in the frontoparallel, or coronal, plane. The arrow indicates the position and direction of the patient's eyes. The solid line with dots indicates the true coronal plane, the broken line with circles shows what the patient assumed to be the coronal plane. In *A* the patient views the threads in the line of regard: in *B* he views the threads 15 degrees to the left, and in *C*, 15 degrees to the right of his original line of regard.

Visual Stimulations Without "Framework."—Even in normal subjects, the structure of visual space may show lability or become distorted if the visual framework is missing or if the postural mechanisms are disturbed. Thus, a single light in the dark has no particular localization, but after a certain period of latency begins to describe illusory motions (autokinetic movements), which may eventually involve the patient's postural organization, so that even a patient's own body, the chair on which he sits or the floor begin to sway and turn in the dark room.

Conversely, a predominance of postural components over purely visual factors in localization is brought out in normal subjects by presenting to them a single luminous vertical line in a totally dark room. If the subject tilts his head to the left, the line will seem to be inclined correspondingly to his right, and vice versa

(Aubert phenomenon). In normal surroundings, a tilt of the eyes, head and trunk will not produce an apparent tilt of the perceived vertical line.

With our patient, autokinetic movements were not at random in all directions of the field, as they are with the normal subject. Instead, the light drifted persistently upward and to the patient's right, or, in other words, away from the most affected region of his field. The Aubert phenomenon was likewise modified, and in the same manner. When the patient tilted his head to the left, the presented vertical line seemed to him to tilt to the right. This is the most usual normal reaction. However, when he tilted his head to the right, the line seemed to him inclined to his right side (and not his left, as expected).

Further tests in a dark room with single stimulus patterns (luminous lines and circles) revealed that the patient's ability to localize objects in his left lower quadrants was frequently beset by the same difficulties that he experienced in daylight.⁴¹

When a single luminous pattern was exhibited alternately to the patient's left lower quadrant and to his right lower quadrant, he pointed correctly on the right, but on the left he pointed considerably to the left and beyond the test object. Thus, even a single light surrounded by total darkness was displaced by the patient in the coronal, as well as in the sagittal, plane. However, under these conditions, the téléopsia was not accompanied with changes in the object's apparent size and shape.

Stereoscopic Tests.—Using a simple refracting stereoscope, the patient obtained binocular fusion and normal depth effects. However, in the lower left sector of the fused image fusion was ill sustained, and the image appeared faded. In the remaining quadrants no abnormalities were reported by the patient.⁴² These results were obtained irrespective of the type of figure used in the fusion tests.

Intellectual Functions Pertinent to Orientation in Space.—The patient was capable of making maps and showed considerable skill in the interpreting of blueprints. (As we have already pointed out, he was able to navigate a plane.) His drawing and copying ability for bidimensional and tridimensional patterns was within normal limits.

However, on certain visual-constructive subtests of the Wechsler-Bellevue scale, the patient was unable to perform according to his intellectual level (as indicated by an intelligence quotient of 126). He exceeded the time limits and failed on surprisingly simple tasks. Especially in block tests, there was a curious tendency for errors to appear in the left half, and most frequently in the left lower sector of the patterns.

41. Maintenance of the patient's forward fixation in the dark room was accomplished by instructing him to face an intermittent sound coming from a source in front of him. Previous tests of auditory localization and associated movements of the head and eyes in this patient had shown that his performance was approximately normal in these respects.

42. It should be borne in mind that even with the normal subject, fusion may be unequally sustained in different sections of the binocular field. Such inequalities may be produced by the use of conflicting contours in the stereoscope. If a horizontal line is presented to one eye and a vertical line to the other, the fused binocular image is that of a cross. In the area of intersection of the two lines, fluctuation in the distinctness of the image will occur. This fluctuation has been interpreted as a sign of binocular rivalry, which can apparently be limited to the area of intersection. Such localized rivalry can be demonstrated not only in the center of the field but in any other portion of the field in which there are intersecting or "conflicting" contours.

Grouping, sorting and other tests of abstract behavior⁴³ failed to reveal any general impairment in his intellectual organization which could have contributed to the specific difficulties in visual space perception. There was no right-left disorientation or apraxia. Except for the changes already noted in the sensory status of the neurologic examination, the patient had no gross disorder of the body scheme.

Comment.—A number of points in this case are worth emphasizing.

1. The disorientation in visual space was largely limited to homonymous (left lower) quadrants of the field of vision.

2. Except for a slight contraction for color, the perimetric fields and tangent screen examinations revealed no gross defects.

3. However, special tests showed that the integrity of the field was only apparent. Procedures such as the measurement of fusion frequencies of visual flicker, determination of thresholds of stroboscopic motion, assessment of phenomenal speed and evaluation of after-imagery disclosed a definite alteration in visual function, particularly in the left lower quadrants, where there was also spatial disorientation.

4. The spatial disorientation occurred in all three dimensions, but it was most pronounced in the sagittal plane. It was thus manifested not as a lack, but as an excess, of "depth," i. e., teleopsia. The teleopsia was accompanied with changes in apparent size and shape.⁴⁴

5. The errors in localization in the affected field were not at random. They followed definite trends, as shown by tests of pointing and bisection of lines. The patient consistently past pointed to the left and beyond the target. In bisecting lines, he always greatly overestimated the peripheral portion of lines presented in his left field of vision. It can thus be inferred that the coordinates of the subjective visual field had undergone a deformation. The presence of such a systematic distortion was further demonstrated by the three string experiment. In this experiment (and under other, similar conditions in which both halves of the field of vision were simultaneously stimulated) the patient's performance suggested that the subjective coronal plane was rotated as a whole. The direction of the rotation of this plane was "away from" the patient on his left and "toward him" on his right. With this, there were occasional alterations in apparent size and shape in the right, as well as in the left, half of the field of vision.

43. Goldstein, K., and Scheerer, M.: Abstract and Concrete Behavior: An Experimental Study with Special Tests, *Psychol. Monogr.* **53**:151, 1941.

44. The observation that teleopsia in the case of unfamiliar objects was associated with an apparent enlargement (macropsia), rather than with micropsia, might have important theoretic implications. However, most of these observations were made with indirect vision. Under such conditions, there is little, if any, constancy of size, even with normal subjects. Comments on the associated changes in size will therefore be limited to the second case, in which similar findings could be obtained, even with macular vision.

6. Conversely, changes in the actual size of the presented object modified the teleopsia. The alterations in the patient's subjective visual space perception were therefore not absolutely constant. They could be influenced, even reversed, by changes in the total stimulus configuration.

7. The more the total stimulus configuration was simplified, the more apparent were the persistent tendencies toward deformation in the subjective coordinates of visual space. When a visual framework was practically absent, as on stimulation with a single luminous target in a totally dark room, the resultant illusory motions of a single light, and illusory inclinations of a luminous vertical line, were always to the right, or away from the implicated (left) region of the patient's field.

8. The case under consideration gains in theoretic significance if one bears in mind that there was no intellectual deficit, no gross spatial disorientation, executive disorder or agnosia.⁴⁵ The perceptual disturbance was practically limited to the field of vision.

9. In spite of the limited nature of the disorder, the extraordinary amount of successful compensation of the defect remains a problem. The patient's performance on tests with the stereoscope may perhaps help to explain it. Under the additional stress of binocular fusion, there were fluctuation and extinction of that portion of the fused image which was exposed to the homonymous left lower quadrants. Possibly this automatic extinction led, in everyday vision, to elimination of the disturbing teleopsia and the associated abnormal perceptions.

In this instance, then, extinction would seem to have a teleologic nature. However, as we have pointed out elsewhere,^{1a} extinction may just as readily lead to serious impairment of vision, as, for example, by changing hemiamblyopia into what amounts to complete hemianopsia.

45. The only inkling of a more serious involvement of gnosis and praxis might be seen in the patient's difficulties with the Kohs block test. His tendency to make errors oftenest in the most implicated (left lower) quadrant demonstrates the close clinical relation between central disorders of vision and defects of "visualizing" (visual memory). One is reminded of Niessl von Mayendorf's unorthodox view (Niessl von Mayendorf, E.: *Zur Lehre von der Seelenblindheit*, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **152**:345, 1935; **159**:284, 1937) that pattern vision proper and "visualizing" (or visual memory) have the same cortical substrate.

(To Be Concluded)

POLIOMYELITIS

Study of an Epidemic of Forty Cases in Key West, Fla., May-August 1946

CAPTAIN W. DALTON DAVIS (MC), U.S.N.

AND

LIEUTENANT (JG) CHARLES M. SILVERSTEIN (MC), U.S.N.R.

ON MAY 23, 1946 an epidemic of poliomyelitis began on the island of Key West, Fla., 120 miles (192 kilometers) from the mainland and 170 miles (272 kilometers) southwest of Miami. During the next month and a half at least 38 cases of clinical poliomyelitis developed, 36 of which were of the paralytic type. One month later, on August 4, 2 other cases occurred.

The population of Key West at the time of the epidemic was about 14,000 civilians and about 3,500 Naval personnel and their families.

Ten of the first 11 patients were treated at Jackson Memorial Hospital in Miami; the remaining 28 patients (except for 2, whose disease developed while they were en route to California) were observed, their illness diagnosed and treatment administered at the United States Naval Hospital in Key West. There had been no previous epidemics of poliomyelitis in Key West, and the average incidence of the disease for the past ten years had been only 1 case per year.

The hospital set up a special poliomyelitis unit for the Key West area. One hundred and ninety persons suspected of having the disease, in addition to the 40 patients with a positive diagnosis, were examined and observed. Of these, 11 were believed to have abortive poliomyelitis, and 22, probable abortive poliomyelitis, and over 100 had symptoms of a disturbance which remained undiagnosed. The last group complained of some combination of the following symptoms: fever, headache, muscular pains, neck ache, backache, dizziness, general malaise, sore throat and transient weakness of an extremity. One or more examinations of the spinal fluid were made on most of these patients, without evidence of the disease. None of these patients, however, is included in the list of 40 patients with clinical poliomyelitis.

From the Medical Service, United States Naval Hospital, Key West, Fla.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

The incidence of verified cases in this epidemic was 2.3 per 1,000, or 230 per 100,000, of the population.

Some of the findings in this epidemic were unusual. The age and sex ratios for the civilian group differed from those for the service personnel and their dependents. Of the 40 patients, 19 were civilians, 16 were dependents of service personnel and 5 were service personnel. Although 17, or 42.5 per cent, of the total number of patients were adults (19 to 33 years of age), 73.7 per cent of the patients in the naval families involved were adults, whereas only 10.5 per cent of the civilian patients were adults.

Thirteen (68.4 per cent) of the patients in the Navy group were in officers' families, although the ratio of officers to enlisted men was about 1:8. Eight of the 19 service personnel and dependents with the disease were wives of officers and 2 were wives of enlisted men.

TABLE 1.—*Distribution of Cases of Poliomyelitis According to Age Groups*

Age, Yr.	Service		Civilian		Total No.	Percentage of Cases
	M	F	M	F		
Under 1.....	1	0	0	0	1	2.5
1 to 2.....	1	1	1	2	5	12.5
2 to 3.....	0	0	0	2	2	5.0
3 to 4.....	1	0	1	0	2	5.0
4 to 5.....	1	0	2	1	4	10.0
5 to 10.....	0	1	3	1	5	12.5
10 to 15.....	0	0	3	0	3	7.5
15 to 20.....	1	1	0	2	4	10.0
20 to 25.....	0	5	0	1	6	15.0
25 to 30.....	1	3	0	0	4	10.0
30 to 33.....	2	2	0	0	4	10.0
Total.....	8	13	10	9	40	100.0

There was a strong history of contact in this group. This aspect will be discussed later. Of the Navy patients, 2 were officers (lieutenant commanders) and 2 were enlisted men, all of whom lived in the city of Key West. The other, a Wave on the hospital staff, lived in the hospital barracks.

Of the 40 patients, 22 were females and 18 males. Of the adults, 13 were women and 4 men. The youngest patient was 7 months old; 4 patients were 30 years of age or older.

Although the expectancy of paralytic poliomyelitis during pregnancy has been given as less than 1 in 1,000 cases of poliomyelitis and less than 1 in 50,000 pregnancies,¹ 6 of the women in this epidemic were pregnant. A seventh was three weeks post partum at the time of admission.

There were 3 deaths (1 adult and 1 child in the Navy group and 1 adult in the Army group), a mortality of 8.3 per cent of the para-

¹ Aycock, W. L.: New England J. Med. 225:405, 1941.

lytic patients. Five of the first 10 patients were respirator patients; there were 7 respirator patients in all.

There were 3 instances in which 2 positive cases occurred in the same family (6 patients). Thirteen of the 34 remaining patients gave a history of febrile illness in one or more members of the family at the same time which, as described, could have been a mild abortive form of the disease. In 3 patients acute symptoms developed just after they left Key West (2 en route to California and 1 to Palm Beach).

No cases were reported among the Negro population. Only 8 of the 19 civilian patients were natives of Key West. All but 1 of these natives were children, all under 5 years of age. The only adult was the pregnant mother of 1 of the patients.

EPIDEMIOLOGY

The frost-free city of Key West, which occupies most of the terminal island of the chain of Florida Keys, is 4 miles (6.4 kilometers) long and 1½ miles (2.4 kilometers) wide. The northeastern half of the island is rimmed by Roosevelt Boulevard. In the northern part of this half of the island is located the large, wartime (civilian and Navy) Poinciana housing project, where 13 cases were reported. The entrance to the island is at this northeastern end, where the Naval Hospital is located. Just below the southeastern end of Roosevelt Boulevard is the small Rest Beach housing project (75 units), limited to Naval officers' families, where 6 of the cases of poliomyelitis developed.

The climate is semitropical.

The milk supply and at least 90 per cent of all other supplies for the various Naval activities and the city come from the Miami district.

It is seldom possible to narrow the mode of transmission of the virus of poliomyelitis to a single factor. Modes of transmission which have had various degrees of importance in the past, and which were considered in this epidemic, were water, food, milk, flies, sewage pollution and direct contact.

Water.—The water supply, delivered by pipe line from Florida City, is chlorinated at the source, rechlorinated en route and again rechlorinated by the city and each naval station before use. The present water line was built in 1944. Before that time the natives had to depend on rain water, which they stored in cisterns. Many of these cisterns are cross connected with the main water lines which enter these homes. Eight hundred to 1,000 cisterns are still in use, and few are properly closed. It is possible that the main water supply may be contaminated by these cistern cross connections: however, samples of water have been tested weekly and have always been found to fulfil the standard requirements of water analysis.

Sewage Disposal.—The main method of sewage disposal is by septic tank or cesspool, since less than 30 per cent of the homes are connected with the sewage disposal lines. Eight civilian and 4 Navy patients lived in homes where sewage was disposed of by a septic tank or cesspool.

Before the epidemic started, the raw sewage was pumped through sewer lines with two outlets: one, on the northeast side of the island, into the Gulf of Mexico, with an emergency by-pass into Garrison Bight Yacht Basin, a shallow, semi-inclosed body of water; the other, extending 600 feet (182 meters) from the southeastern end of the Key into the Atlantic Ocean near South Beach, Fort Taylor Officers' Club Beach and Rest Beach, which are the island's principal bathing beaches. Tidal action is slight here, and gross sewage was often observed close to shore. Subsequent to the onset of the epidemic the sewage was pumped into settling tanks and the effluent chlorinated; pumping of sewage into Garrison Bight Yacht Basin was discontinued.

Garbage.—Both wet garbage and trash are hauled to a "dump" near United States Highway no. 1 on Stock Island, the next proximal Key. An attempt is made to burn and to bury the collection with one bulldozer; most efforts at burial are futile, since part of the "dump" is on swampy land. Garbage is collected once a week except in the federal housing units, where it is collected three times a week. In the housing units most garbage cans have poorly fitting lids, and the cans often overflow. In the city, most of the lids of the garbage cans were missing; others were badly bent.

Milk.—The milk, which is supplied by two dairies, is tested regularly. It is trucked in from the Miami area.

Flies.—Flies are prevalent throughout the city, but not in larger numbers than usual. Chickens, horses and numerous dogs and cats are kept, improperly, within the heavily populated parts of the city.

A Navy plane began spraying the island with DDT (4,4'-dichlorodiphenyltrichloroethane) as soon as the epidemic started. This spraying has been continued at frequent intervals and has greatly reduced the fly and mosquito population.

EPIDEMIOLOGIC HISTORY

Repeated "direct contact" was the most obvious and important common denominator in at least 18 of the cases, which included five small groups of patients. In other cases, flies and poorly handled garbage seemed to be particularly incriminated.

Swimming in polluted water was another distinct etiologic possibility. Eighteen of the 40 patients had been bathing at Rest Beach or South Beach during the two or three weeks preceding the onset of

their illness. (For 9 patients information on this point was not available.) These two beaches, where tidal action is slight, were located near the sewage outlet.

Table 2 gives the results of bacteriologic examination of samples of water from the principal beaches and swimming pools in this area.

Since this analysis, the sewage effluent has been chlorinated, and at the present time samples show no evidence of pollution. Swimming was prohibited at all service pools and at the Officers' Club beach as soon as the epidemic began.

The occurrence of over 1 colony of the gas-forming *Escherichia coli* (*Bacillus aerogenes*) group per 100 cc. sample from deep salt water and more than 5 colonies per 100 cc. sample from surface water is evidence of pollution. It is to be noted that from all the sites except Municipal Pool, Naval Air Station Bathing Beach and the Naval Hospital the water showed gross pollution. The greatest pollution

TABLE 2.—*Bacteriologic Examination of Water (July 22, 1946)**

Salt Water (100 Cc. Samples) Collected from	Final Presumptive Test, Cc.				Confirmatory Test, Cc.			MPN †
	10	1.0	0.1	0.01	10	1.0	0.1	
Rest Beach Pond.....	5+	3+	0	0	5+	3+	...	79
Municipal Pool.....	0	0	0	0
Weaver's Cabins.....	5+	3+	1+	0	5+	3+	1+	110
Poinciana Lake.....	5+	5+	0	0	5+	5+	...	240
Rest Beach.....	5+	4+	4+	0	5+	4+	4+	350
Officers' Club Beach.....	5+	5+	3+	0	5+	5+	5+	920
Garrison Bight Yacht Basin.....	5+	5+	4+	0	5+	5+	4+	1,600
Naval Hospital.....	0	0	0	0
Naval Air Station Bathing Beach.....	0	0	0	0

* Furnished by the Miami Branch State Board of Health.

† MPN means maximum probable number. Other values are expressed as the number of colonies.

(expressed as the maximum probable number) occurred in Garrison Bight Yacht Basin and the Officers' Club, which are in closest proximity to the sewage outlets.

The last important factor seemed to be visits to Miami, where there were a number of cases of poliomyelitis. Thirteen of the patients had either been in Miami within the preceding three weeks or had had Miami visitors in their homes. At least 5 of the patients' apparently contracted their disease in Miami. Miami, Fla., and Habana, Cuba, were the two cities of size nearest Key West. The epidemic in Key West began on May 23, when the peak of the Miami epidemic was reached. There was also an epidemic at this time in Cuba (90 miles [144 kilometers] away by air). In the next six weeks 37 verified cases developed. The cases were fairly evenly distributed throughout this period. The longest interval between the appearance of cases was five days. The greatest number of cases to appear in one day was 5.

A month after the epidemic was apparently over, 2 new cases, those of a man and a pregnant woman, occurred.

The development of the epidemic may be briefly sketched.

The first patient, a 2 year old girl, was the daughter of an iceman who had been making regular trips to Miami to visit his wife (who had a febrile illness not diagnosed as poliomyelitis). This patient lived in downtown Key West.

Eight of the next 9 patients (cases 2, 3, 4, 6, 7, 8, 9 and 10) were from the Poinciana area. Five of these 8 patients (all children) had played together frequently and had become ill with clinical signs of poliomyelitis about the same time. Three of them had played near a large pool of stagnant water in the backyard, which was subsequently condemned by the city. Three had been in swimming at Rest Beach or South Beach. Three had made recent visits to Miami or had had visitors from Miami.

The patient (case 5) who did not live in Poinciana was the wife of an officer aboard one of the submarines and lived at Rest Beach: Ten days later the executive officer aboard the same submarine, a friend of this patient, had onset of acute bulbar poliomyelitis (case 17). Significantly, two months later the wife of an enlisted man on the same submarine was admitted with poliomyelitis (case 39). The families of patient 5 and patient 17 were in frequent contact. The children of patient 19 played frequently at the home of patient 5. Two weeks after patient 5 was admitted, patients 19, 20 and 21 were admitted with acute preparalytic poliomyelitis. These 3 patients were pregnant women, good friends, 2 of whom were next door neighbors at Rest Beach; the third lived in Poinciana. They had been at parties together and were frequent visitors at each other's homes. Ten days after patient 19 exhibited acute symptoms of poliomyelitis, her husband (case 28) presented acute symptoms of the disease and died five days later, of the bulbar form.

Patient 11 was the wife of an enlisted Navy man. She had been in Miami two days before the onset of her illness. She had no history of contact, nor did patients 12 and 14 (both children). Patient 12, a 10 year old boy, had arrived in Key West from New York three weeks previously. There were many flies about their premises, a horse next door and goats across the street. The patient had been in swimming at South Beach.

Patient 13, another child, gave no history of contact, but eleven days later a waitress (case 15) who had lived in the same apartment house with her became ill with poliomyelitis. The waitress had recently visited in Miami and had swum at South Beach. A son of a steady customer was said to have had poliomyelitis. Fifteen days after patient 13 had the onset of poliomyelitis, a child across the street (case 27) also became ill with the disease. The latter child's father ran a lunchroom.

Whereas 12 of the first 14 patients were children, 6 of the next 7 patients were adults. Patient 15, the wife of a commander aboard another submarine, began to have prodromal symptoms while on a visit to Miami and exhibited acute symptoms eight days after returning to Key West. On the day she was admitted to the hospital, the 17 month old son (case 16) of the executive officer aboard the same submarine was admitted with poliomyelitis. As a matter of fact, the boy (case 16) frequently visited her home. Significantly, no other cases were reported from the families of men aboard this submarine.

Patients 22, 24 and 27 had no known contacts. They had swum at Rest Beach. Each of these patients had chickens on the premises or next door and many flies. Case 23, that of a 2 year old girl, was interesting, since her parents claimed to have isolated her strictly on the day the first case of poliomyelitis was reported

in Key West. She drank boiled milk and water, was allowed no visitors and was not permitted to be outside. The family raised chickens. Garbage cans were sprayed with DDT. Two doors away, however, there was a filthy yard, with many flies.

Patient 25 gave no history of contact. His parents had been in Miami three weeks previously, and he had been to nursery school in the Poinciana area.

Patient 26, an Army private who lived in Poinciana, gave no history of contact. He had been on a fishing party, where every one drank from the same bottle of water. One of his companions on the party subsequently came down with what was thought to be abortive poliomyelitis.

Patients 29, 31 and 32 all became ill about the same time. Patients 29 and 32 were a native boy, aged 3 years, and his mother (in her third trimester of pregnancy). Patient 31 was a near neighbor's son, who visited frequently at her home and who, three weeks previously, had just moved to Key West from Miami.

Patient 30 was a 19 month old baby from Rest Beach who, three weeks before, had moved over from Poinciana.

Patient 33, an officer's wife, was admitted three weeks after delivery. She had been visited in the hospital by the mother of a patient with poliomyelitis about seventeen days prior to admission. It was subsequently known that her husband had a febrile illness, with headache and stiffness of the neck and back for three days, but he did not consult a doctor.

Patient 34, a Wave who lived in the hospital barracks, returned from a fourteen days' leave four days before she became ill. She had been in Miami two days. She had swum at Rest and South Beaches. She had dated the Army physician, who, eleven days previously, had examined and admitted patient 26. Her roommate had the onset of probable abortive poliomyelitis three days after she was admitted. Significantly, this was the only case of typical abortive poliomyelitis seen among members of the hospital staff.

Patient 35, an officer's wife, recently treated for menorrhagia and "influenza," presented acute symptoms on the way to Palm Beach. Her husband daily brought home from work the husbands of patients 20 and 21.

Patient 36, the pregnant wife of a medical officer at the submarine base dispensary, had been in the hospital two weeks previously with an attack of pyelitis. There was no history of contact. She had been swimming at Rest Beach regularly.

Patients 37 and 38, sons of a commanding officer of another submarine, had been strictly isolated at home ever since the epidemic began. They remained at home and were allowed no visitors. However, their parents had been in Miami two weeks before their children exhibited acute symptoms. These children were leaving this area to escape contagion, but became ill with the disease en route to California.

Patient 39, the pregnant wife of an enlisted man, aboard the same submarine as the husbands of patients 5 and 17, gave no history of contact. She became acutely ill one month after the last reported case. She had not been swimming. She had stayed at home and avoided crowds. She had, however, attended a dance three weeks prior to her admission. Garbage and sewage disposal was satisfactory.

Patient 40 was a chief at the submarine base. His wife had had a febrile episode with stiff neck about ten days before. He had been swimming regularly at South Beach twice a week.

From the standpoint of possible incrimination of flies and garbage, it is interesting to study the east to west spread of poliomyelitis in Poinciana, the earliest and largest single area hit (13 cases). There are four groups of dwellings in this area.

To the east is Poinciana Place (a housing project of 210 dwelling units), in the region of which 8 cases developed. Near this project, to the east, there is a stable of horses, goats and poultry, where flies breed in large numbers. The prevailing breeze is from the east or southeast. The first group of cases (2, 3, 4, 6, 8 and 10) came from this area. Adjoining, westward, is Poinciana Extension (a project of 550 dwelling units), where only 1 case (26) developed, three weeks later. Farther west are West Poinciana (with 140 housing units), where the next 2 cases (7 and 9) developed, and the MacArthur Homes, cases 16 and 17 being reported in this and in the adjoining area.

It is noted that the largest housing project (550 units) had the least number of cases (1). On inspection, this project had much fewer flies than did the other areas. For example, no fly larvae were found in Poinciana Extension, while about 25 per cent of the garbage cans in West Poinciana contained fly larvae.

Practically all these units have the same water supply and the same sewage system and receive milk from the same dairy, and the tenants have the same social and financial status, suggesting that these factors were not incriminated in the epidemic.

It is also to be noted that in the two other housing projects, Porter Place (136 units) and Fort Village (158 units), no cases were reported. Their location was far removed from the Poinciana and Rest Beach areas.

At the homes of 15 of the 24 patients not from the Poinciana area, the garbage and fly situation, either on the premises or next door, was described as "bad." Garbage cans often contained many maggots.

Thus, direct contact, flies and the beaches (polluted water) could not be excluded as important factors in the local spread of the disease.

PREDISPOSING FACTORS

The influence of various conditions on the susceptibility to poliomyelitis has been much discussed. It has been claimed, for example, that a recent tonsillectomy may provide an easy path of entry for the virus, predisposing particularly to bulbar involvement. None of the 40 patients in this series had had a tonsillectomy in the past two years. Increased fatigue or excessive exercise is said to be a predisposing factor. Four patients gave a history of recent excessive work or exercise.

It has been noted that people who have poliomyelitis are usually well nourished and healthier than the average. All but 4 of the patients could be considered as well nourished, better than the average. Three had had recent illnesses (patient 36, pyelitis with pregnancy, two weeks previously; patient 35, fever following immunizations, four days previously). One patient was malnourished and had been drinking heavily prior to admission. One patient was recently parturient.

The influence of pregnancy on susceptibility to poliomyelitis is not known.¹ The incidence in this epidemic (6 pregnant and 1 parturient patient, or 17.5 per cent of the series) is the highest ever reported in an epidemic of poliomyelitis. In 1945 Fox and Sennett² stated that only 85 cases of the disease in pregnant women had been reported in the literature.

Aycock³ expressed the belief that the endocrine glands may influence resistance or susceptibility to poliomyelitis. He injected poliomyelitis virus intravenously into castrated female monkeys and into normal controls. Some of the castrated monkeys were prepared by receiving a course of estrogen therapy. He reported that the estrogen-prepared animals showed a significantly increased resistance to poliomyelitis and that in the monkeys which did succumb the onset of the disease was delayed. He also showed that a group of poliomyelitic patients had a higher urinary excretion of estrogens than did the normal controls.

Why, then, do not the higher amounts of estrogen in pregnancy protect the patient? The answer seems to be that the hormonal status of the pregnant woman differs from that of the nonpregnant woman, as well as the castrated animal. While estrogens increase in pregnancy, pregnancy is dominated rather by progesterone (produced by the corpus luteum and by the placenta). Estrogen and progesterone are physiologically antagonistic. Since other normal secretions, such as that of the pituitary gland, are also increased during pregnancy, the end effect of several interacting variables, including increased estrogen, may differ from the effect of increased estrogen alone.

The effect of estrogen may be pronounced, or more unopposed, during the first trimester. This might explain Weaver and Steiner's⁴ report that 3 of 13 rats inoculated during the first trimester of pregnancy resisted infection with poliomyelitis virus, whereas all animals inoculated in the second or third trimester, as well as virgin animals, were uniformly susceptible. It might explain the incidence of poliomyelitis in 75 women (cited by Weaver and Steiner⁴) distributed according to trimesters: first trimester, 17.1 per cent; second trimester, 34.3 per cent, and third trimester, 48.6 per cent. Of our series, 1 patient was in the first trimester; 4 were in the second, and 2 were in the third. Was the onset of the disease delayed in the pregnant woman? It is not possible to say. However, 4 were among the last 8 patients to be admitted. The other 3 were admitted in midepidemic. The only case occurring in the first trimester was case 39 (in the ninth week of pregnancy).

2. Fox, M. J., and Sennett, L.: *Am. J. M. Sc.* **209**:382, 1945.

3. Aycock, W. L.: *Endocrinology* **27**:49, 1940.

4. Weaver, H. M., and Steiner, G.: *Am. J. Obst. & Gynec.* **47**:495, 1944.

A factor common to all the pregnant patients (6 Navy wives and 1 civilian) in this series was their abundant use of vitamin supplements. Five other patients took additional vitamins regularly; 5 did not; for the rest information on this point was not available. This observation is of some interest, since Foster and associates,⁵ in experiments with mice maintained at various levels of thiamine intake, reported that the incidence of paralysis for mice given injections of murine poliomyelitis virus (Lansing strain) was several times as high on the high thiamine diet as on the thiamine-deficient diet. Similar observations were made by Rasmussen and associates.⁶ In some instances in which thiamine-deficient mice were subsequently given adequate thiamine they became paralyzed after a prolonged incubation period. Partial starvation of the animals on a complete diet also increased the resistance of mice to the virus, but it was demonstrated that the vitamin deficiency exhibited a greater protection than did the restriction of food intake, indicating that the effect of the vitamin deficiency could not be entirely due to inanition. Induced deficiencies of riboflavin, pyridoxine, protein and tryptophan had no effect on the resistance.⁷

Draper⁸ described a certain constitutional type of child as susceptible to poliomyelitis. Briefly, children who become ill with poliomyelitis are large for their age; they are all broad faced children, with high cheek bones. Their eyes are wide set. The space between the inner canthi is also wider than normal, so that the whole expression is that of a flat-faced, broad, almost Icelandic type. In addition, there is a definite design of the bony skeleton, especially of the skull and hands. The gonial angle between the posterior border of the ascending ramus and the inferior border of the horizontal ramus of the mandible is wide, and the subcostal angle is narrow. The teeth are large for the size of the face and are usually irregular.

This disease occurs almost entirely in brunets. If one observes the blond patients closely, one will find that they are covered, in many cases literally covered, with deeply pigmented spots. The mothers of many patients with poliomyelitis are thyroid types. The fathers are often of the eunuchoid, giant form of the Fröhlich type. The genital inadequacy of the boys with poliomyelitis is striking.

5. Foster, C.; Jones, J. H.; Henle, W., and Dorfman, F.: *Proc. Soc. Exper. Biol. & Med.* **51**:215, 1942; *Science* **97**:207, 1943; *Am. J. M. Sc.* **205**:465, 1943; *J. Exper. Med.* **79**:221, 1944.

6. Rasmussen, A. F., Jr.; Waisman, H. A.; Elvehjem, C. A., and Clark, P. F.: *J. Infect. Dis.* **74**:41, 1944.

7. Jones, J. H.; Foster, C., and Henle, W.: *Am. J. M. Sc.* **211**:245, 1946.

8. Draper, G.: *Acute Poliomyelitis*, Philadelphia, P. Blakiston's Son & Co., 1917.

Patients 16 and 27 fitted Draper's description well. However, the description was of little clinical aid. Five of the patients had blond, or almost blond, hair and fair complexion; 4 others were of fair complexion and had light brown or brown hair.

It has been suggested that some families are constitutionally more predisposed than others to diseases of the nervous system. Surprisingly, 3 of the patients reported the previous incidence of poliomyelitis in their families. The aunt of patient 14 was a victim of poliomyelitis in Key West seven years ago. The nephew of patient 20 and the sister of patient 24 also were said to have had poliomyelitis.

PERIOD OF INCUBATION

About one-half the 40 patients gave a history containing clues to the length of the incubation period. For example, patient 28, who died of bulbar poliomyelitis, had the onset of acute symptoms seventeen days after his wife's (case 19) prodromal symptoms and ten days after she became acutely ill. Patient 19 was admitted with acute symptoms fifteen days later than patient 5, at whose home her children played. Patient 12 had moved to Key West from New York less than three weeks before he became ill. Patient 15 had returned from a week-end visit to Miami ten days before she became ill. Patient 33 was visited, in the hospital after the birth of her baby, by the mother of a patient with poliomyelitis almost three weeks before she became sick.

On the basis of such reasoning, the period of incubation ranged from seven to twenty-two days for this group of patients, with an average of about two weeks. This is about the average usually ascribed to cases of the paralytic type. The range of the incubation period is usually given as five to thirty-five days.⁹

CLINICAL OBSERVATIONS

Symptoms.—Four fifths of the patients had a definite prodromal period of from one to eight days (for 1 patient, three weeks). Oftenest the prodromal period was one to four days and consisted of some of the following symptoms: general malaise, weakness, fever, irritability, fatigue, sore throat, muscular pains, insomnia, headache, dizziness and nausea.

The presenting acute complaint depended on the stage at which the patient was first seen. Three fourths of the civilian patients (mostly children) were first seen in the paralytic stage; hence, a limp or inability to walk was the commonest complaint of these patients, together with

9. Rasmussen, A. F., Jr.; Waisman, H. A.; Elvehjem, C. A., and Clark, P. F.: *J. Bact.* 45:85, 1943.

fever and headache. Over one-half the Navy patients (largely adults) were seen in the acute, preparalytic stage. An additional one-fourth were first seen with minimal prodromal complaints, so that the natural course of events in this disease was clearly demonstrated.

The onset of acute symptoms was gradual in 35 patients. The other 5 patients first noted the symptoms on awakening in the morning. The earliest acute symptoms were usually mild fever, headache, sore throat, backache, neck ache, malaise and vomiting. Headache (severe in 4 patients) was the commonest complaint, being recorded for 27 patients. Only 4 patients reported having had no headache. (The 9 other patients were small children.) All but 1 of the adults complained of headache. The duration of headache before admission varied from one to eight days, usually from one to three days.

Malaise, drowsiness, irritability and restlessness were frequent complaints. Only 3 patients claimed not to have these symptoms. Nine patients complained of all four.

The highest temperature before admission was said to be 105 F. The temperature on admission depended partly on the stage at which the person was seen, since the temperature is usually highest in the acute, preparalytic stage. The highest temperature on admission was 104 F.; the average was a little above 101 F. Seven patients had a normal temperature (under 98.6 F. orally, or under 99.6 F. rectally) on admission; the disease of 2 of these was in the preparalytic stage. (After admission the temperature of 1 of these 2 patients rose from 98.4 to 101 F.; that of the other, from 98 to 100 F.) This is an important point in an epidemic. Since fever is usually one of the cardinal signs of an infection,¹⁰ a patient suspected of having poliomyelitis who has no fever, but mild symptoms, may be prematurely dismissed. In a suspected case, it is worth while to inquire routinely about recent fever, although the temperature at the time of examination is normal.

CASE 40.—An enlisted man aged 33 was seen on August 6, complaining of moderate headache and slight stiffness of the neck. Eight days before admission he first began to feel malaise. During the next five days he complained of indigestion, fatigue, absent-mindedness and continued malaise. Three days before admission there developed a severe headache, which went away after an hour and returned the same night, along with fever (which his wife first noted). Two mornings before admission he became nauseated, and his back and neck felt stiff and hurt slightly on flexion. Examination by the dispensary physician was said to have shown nothing abnormal at the time. At the time of admission, at his wife's insistence, his headache, backache and neck ache were gradually disappearing and, except for the mild headache, he was comfortable. He had had no fever in two days. Ten days before his wife had complained of fever and stiffness of the neck.

Examination.—The temperature was 98.4 F., the pulse rate 72 and the respiratory rate 22, per minute. Examination revealed nothing significant except for some

10. Discussion on Aycock, W. L.: A. Research Nerv. & Ment. Dis., Proc. (1931) 12:114, 1932.

pain in the midback when the patient bent his head between his knees. There was no limitation of action. The reflexes were normal.

Laboratory Data.—The spinal fluid contained 521 white cells (18 polymorphonuclear leukocytes and 503 lymphocytes). The white blood cell count was 6,000, with 46 per cent polymorphonuclear leukocytes and 54 lymphocytes. The sedimentation rate was 6 mm. in one hour (Westergren method).

Course in Hospital.—The day after his admission the patient's headache almost completely disappeared. He has been asymptomatic except for mild malaise. He is limber, and no subsequent weakness or paralysis has developed (this case is the second nonparalytic one in the present series).

The patient may give no history of fever, despite its presence. Patient 21, a woman aged 23, had a temperature of 101.8 F., and patient 10, aged 14, a temperature of 102 F., on admission; yet neither had experienced the sensation of fever.

In this series, fever was present from one to twenty-one days before admission, usually from one to three days. There were 9 instances of recurrent fever (two episodes). The duration of fever was from no to nine days after admission, with an average of about four days. Five children had a low grade "fever" throughout their three weeks or more in the hospital (up to 100 or 100.6 F. daily, rectally).

The highest temperature was 107.6 F. (rectal), recorded in the case of patient 26, who died of the ascending Landry type of spinobulbar poliomyelitis, seven days after admission.

Only 4 patients noted chills. Sore throat, occasionally severe, occurred in at least 18 patients. Fifteen patients (including 4 of the 6 pregnant women) complained of nausea and vomiting; 8 other patients experienced only nausea. Only 2 of the 40 patients had definite diarrhea, but 3 others reported loose or slightly increased bowel movements. Seven patients complained of constipation. All but 2 of the patients gave a history of slight to moderate neck ache and backache and stiffness prior to admission. Five children complained of abdominal pain. Dysphagia was present initially in 4 patients; regurgitation of fluids, in 2; dysuria or oliguria, in 4 (not including the pregnant women); aphonia or dysphonia, in 2, and tremors, in 3. Fourteen patients complained of stiffness or pain in muscles other than those of the neck and back.

Other Physical Findings on Admission.—The pulse rate was under 90 per minute for 25 of the patients and rose as high as 160 and 178, respectively, for 2 of the other (adult) patients. The respiratory rate was usually normal. Stiffness of the neck and back was usually present, varying from slight to extreme. Three of the patients had no stiffness or pain on motion of the neck and back at any time. The stiffness was usually much less than that encountered with meningitis. Kernig and Brudzinski signs were noted in only 7 patients. Eight patients (3 small

children and 5 adults) had only slight stiffness, which, particularly in small children, might have been overlooked by the inexperienced examiner. Indeed, early in the epidemic, the Foundation's physiatrist demonstrated stiffness of the muscles of the back of a month old baby which was entirely missed by the medical officer, who had not been in an epidemic of poliomyelitis before.

Sixteen of the patients had mild to severe pharyngitis. For 3 the pharyngitis was pronounced and dominated the clinical picture on admission. A mild degree of associated cervical lymphadenopathy was noted in only 4 patients. Six patients had prominent respiratory signs, including dyspnea, tachypnea, respiratory splinting and abdominal breathing. Two thirds of the patients exhibited weakness or paralysis (of the extremities, vocal cords, muscles of swallowing or muscles of respiration) on admission. In the small children, of course, partial weakness was sometimes difficult to demonstrate.

Reflex changes were only occasionally of value in making an early diagnosis or in predicting the site of involvement. In 11 patients the reflexes were entirely normal on admission. Four others had generally hyperactive reflexes. When the reflexes were hyperactive, they were more often bilateral than unilateral. Unilateral diminution or increase in reflexes was occasionally of aid in the early detection of muscular weakness. In the preparalytic stage, the reflexes in an involved limb were usually at first hyperactive, later becoming diminished or absent. The abdominal reflexes and the knee jerks showed the most frequent changes (24 patients).

In 18 patients hyperirritability and tremulousness were prominent. Four of the patients had definite tremors and involuntary grimacing. Intense hyperesthesia was noted in 2 patients.

COURSE

The length of the acute stage was usually from three to ten days. The end of the acute stage was defined as the time at which the progression of paralysis or acute symptoms had ended and the elevation of temperature and other signs due to the poliomyelitis had subsided, with return to or toward normal.

The period between the onset of acute symptoms and that of paralysis was from one to three days for all but 5 of the patients: For 1 of the latter it was eight days; for another, twenty-four days.

The number of days of progression of the paralysis was usually from one to three (with an average of two days). Only in 1 case was it definitely longer than four days.

CASE 31—A 7 year old white boy was admitted to the hospital on June 30 with headache, fever and aphonia. His illness had begun three days previously with the onset of fever. Headache, fever (temperature, 100 to 102 F.) and drowsi-

ness continued until his admission. Eighteen hours before admission he became unable to talk and had slight dysphagia. There were no other symptoms.

Related History.—The patient had moved to Key West from Miami three weeks before onset of the present illness. Two persons in close contact with the boy (patients 29 and 32) had poliomyelitis. The family used a septic tank. At the neighboring house "ripe" garbage with heavy breeding of flies was found.

Physical Examination on Admission.—The temperature was 103 F., the pulse rate 120 and the respiratory rate 45. The blood pressure was 120 systolic and 70 diastolic. The patient was well developed and well nourished. He was in a semicomatose state and breathed abdominally. There was no stiffness of the neck or back. The reflexes were not recorded.

Laboratory Data.—The spinal fluid contained 31 white cells (3 polymorphonuclear leukocytes and 28 lymphocytes). The protein content was 15 mg. per hundred cubic centimeters. The white blood cell count was 8,600, with 63 per cent polymorphonuclear leukocytes, 35 lymphocytes and 2 per cent eosinophils. The urine showed a slight trace of albumin.

Course in the Hospital.—The patient remained semicomatose during the first twenty-four hours but was able to void and take a few sips of fluid by mouth. His nail beds were slightly cyanotic. The next day his temperature dropped to 100 F. and he appeared more responsive. The following day his color and dysphagia improved and he responded to questions. He steadily improved and was able to stand, with uncertain balance, on July 4 (four days after his admission). The next day muscular evaluation showed no obvious weakness. On July 10 he complained of soreness in the back and pain in the hamstring muscles of the right leg on walking. Spasm was present in this group of muscles, as well as in the right calf. The next day there was no pain, but the muscles of the hamstring group were weak. During the next three days he walked with a limp, but with hot packs, whirlpool baths and passive exercises the affected limb rapidly improved, and by July 18 it was entirely normal again. He exhibited no residual sign and was discharged on July 20.

MUSCULAR INVOLVEMENT

Paralysis of various muscle groups was transient in 4 patients (two days to two weeks). In 6 other patients weakness apparently disappeared after a month. Five patients had no apparent paralysis. In the remaining 22 patients paralysis is still present.

Ten patients had transient or prolonged bulbar involvement of one or both upper extremities in the earlier part of the epidemic. There were 3 deaths among the 8 patients who had had bulbar involvement for more than twenty-four hours, a mortality of 37.5 per cent. Death occurred one, three and five days after admission, respectively. In the earlier part of the epidemic, 6 of the first 11 paralytic patients had involvement of the left upper extremity alone. None of the patients since that time had involvement of the left upper extremity alone. The average number of extremities involved in cases of transient or prolonged paralysis was two (1.9 per cent).

Four patients had involvement of all four extremities. Patient 26 had acute ascending and descending paralysis, ending in death.

CASE 26.—An army private aged 19 was admitted on June 19, complaining of sore throat, fever, headache and malaise. He had been well until seven days before admission, when he felt ill, was lethargic and experienced moderately severe headache. These symptoms had continued. Two days before admission he began to have sore throat and fever. His neck and back became moderately stiff and uncomfortable. The patient's sister had had poliomyelitis four years previously.

Physical Examination on Admission.—The temperature was 100 F., the pulse rate 104 and the respiratory rate 28, per minute. The blood pressure was 120 systolic and 76 diastolic. Examination revealed moderate rigidity of the neck and, to a less extent, of the back. There was bilateral tightness of the muscles of the hamstring group. The reflexes were generally hyperactive. There was a general feeling of weakness but no muscular weakness.

Laboratory Data.—The spinal fluid (June 19) contained 179 white cells, with 31 polymorphonuclear leukocytes, and 148 lymphocytes. The protein content was 50 mg. per hundred cubic centimeters. On June 23 the cell count of the fluid was 230, with 2 polymorphonuclear leukocytes and 228 lymphocytes.

Course in Hospital.—The next morning, June 20, the stiffness of the neck and back had become more pronounced, and weakness of the right arm had developed. The patient began to vomit frequently. He complained of difficulty in swallowing and inability to take a deep breath. His right arm became limp on June 21, and he had pronounced dysphonia and dysphagia. Respirations were irregular. He obtained little relief from increasing dyspnea in an oxygen tent. His left arm became flaccid. He complained of pain in the chest and throat and was unable to take a deep breath. His respirations became more regular, and he was placed in a respirator (with oxygen), with much relief. His color was mildly cyanotic, however. Constant suction had been employed and atropine administered for removal of mucus. He began to have difficulty in moving his legs and was unable to void. The next day, June 22, his temperature rose from 98 to 104 F., and he became semicomatose. He became unable to move his legs or arms. He had been given penicillin therapy as a prophylactic measure. His color was constantly cyanotic. On June 23, he still brought up some mucus, had great difficulty in breathing (even in the respirator) and became comatose. Spinal puncture was performed, with the patient in the respirator. Treatment was continued with oxygen, suction, fluids, enemas and catheterization. He died the next day.

Case 15 is an example of the acute ascending Landry type, which stopped just short of the medulla (transient facial paralysis, dysphagia and dysphonia). The patient has now been two months in an "iron lung," with nearly complete flaccidity of all four extremities and involvement of the muscles of respiration. Her paralysis was complete within twenty-four hours after it began.

Inability to void was present from one to two days in 4 patients, three days in 1 patient and from six to seven days in 4 patients. The last 5 patients included 4 of the pregnant women and the 1 parturient patient.

LABORATORY DATA

Spinal Fluid.—The number of cells in the spinal fluid bore no relation to the severity of the disease, and was only roughly correlated with the clinical degree of meningeal "irritation." For example, patient 21,

who had only slight stiffness of the back and neck, had 428 cells per cubic millimeter and only mild involvement of the lower extremity. Patient 40, who had only slight discomfort in the midback on bending, had 521 cells per cubic millimeter of the spinal fluid and no weakness or paralysis. Patient 24 had a rigid, "poker" back and 171 cells but had never experienced any weakness.

After a great number of examinations of the spinal fluid of persons who were suspected of having the disease but who had almost minimal symptoms and signs (for example, a member of the patient's family), it became apparent that in the absence of signs of meningeal "irritation" the spinal fluid would be normal, even if the history was suggestive of the disease. However, careful watchfulness for slight meningeal changes was necessary.

CASE 34.—A Wave had questionable stiffness of the neck and back when she was first seen. She was not sure that she had had any fever (98.8 F.). Because of a headache of three days' duration and aching in the shoulder muscles, she was admitted for observation, and a spinal puncture was performed. The fluid contained no white cells; the protein content was 15 mg. per hundred cubic centimeters. Nine hours later there were definite stiffness in the lower part of the back, discomfort on flexion of the neck and hyperactive abdominal reflexes. Spinal puncture at that time revealed 23 white cells per cubic millimeter, all of which were lymphocytes. Three days later weakness developed in the right lower extremity.

In the series of 40 patients, the cell count of the spinal fluid varied from a low of zero (3 cells per cubic millimeter on repeated taps) to a high of 563 per cubic millimeter. Six patients had over 400 cells per cubic millimeter, the average being 151 cells. This value is higher than the usual range given for poliomyelitis (15 to 150 cells per cubic millimeter). Seventeen, or less than one-half, had less than 100 white cells per cubic millimeter; only 1 patient had less than 10 cells.

Merritt and Fremont-Smith¹¹ found that the highest white cell count occurs in the preparalytic stage, with the cells predominantly of the polymorphonuclear type. After the onset of paralysis there is sooner or later a shift toward a predominance of lymphocytes. The present findings are in agreement. All but 2 of the patients in the preparalytic stage (on admission) showed predominance of polymorphonuclear cells. In addition, one third of the paralytic patients showed predominance of polymorphonuclear leukocytes. Three patients had 97 per cent or more polymorphonuclear cells (97 per cent of 405 cells, 97 per cent of 428 cells and 98 per cent of 171 cells, per cubic millimeter). Two others had over 90 per cent polymorphonuclear cells. The fact that many of these patients were seen unusually early in the course of the disease and were followed closely may account for the observation of a high per-

11. Merritt, H. H., and Fremont-Smith, F.: *The Cerebrospinal Fluid*, Philadelphia, W. B. Saunders Company, 1937, p. 130.

centage of polymorphonuclear cells. Repeated examinations of the spinal fluid were not made routinely.

The protein values were of interest. Eight of the 10 patients sent to Jackson Memorial Hospital had elevated protein levels (over 40 to 45 mg. per hundred cubic centimeters). However, only 2 of the other patients had an increased protein content of the spinal fluid. This result may have been due to use of a faulty reagent.

The sugar and chloride levels were normal, and no organisms were cultured from the spinal fluid in any case.

Blood.—Slightly over one-half the patients had a normal blood count; the remainder had a mild leukocytosis. Only 3 patients had a white cell count of over 12,000, 2 of these having the bulbar form of the disease. The highest count, 17,400, was that of a child who also had an acute streptococcic throat. The differential count was usually normal. Four children had a relative lymphocytosis, the number of lymphocytes varying from 63 to 78 per cent. No atypical lymphocytes were seen.

DIFFERENTIAL DIAGNOSIS

There were few problems in differential diagnosis. Conditions to be differentiated from poliomyelitis were acute pharyngitis, gastroenteritis, torticollis, septicemia, infectious mononucleosis, meningitis, pregnancy and hysteria.

CASE A-5.—An enlisted man aged 24 was admitted on June 28 for observation for suspected poliomyelitis, with the complaint of backache of one day's duration. After lunch he had noticed weakness and dizziness on bending over. In the afternoon a slight headache appeared, and the patient began to have moderate discomfort and slight stiffness in the small of his back; in the evening he became feverish, and his legs began to feel weak. The related history was without significance. One of his close friends had recently been suspected of having poliomyelitis.

Physical Examination.—The temperature was 101.6 F., the pulse rate 82, and the respiratory rate 21. Examination revealed nothing significant except for slight stiffness and discomfort of the lumbar region. The reflexes were normal.

Spinal Fluid.—The spinal fluid contained 1 white cell (lymphocyte) per cubic millimeter and 15 mg. of protein per hundred cubic centimeters.

Course in Hospital.—On June 29 his shoulder muscles ached and his headache increased. There was increased stiffness in the lower part of the back, which continued the next day. On July 1, the aching in the shoulder had abated, but the patient still had mild generalized headache. On second examination the spinal fluid was normal (no white cells, 10 mg. of protein per hundred cubic centimeters). The temperature was normal at this time, and the patient felt that he was ready for duty on July 2. On standing, however, his headache and backache returned, and he was kept in the hospital until July 6 before being discharged.

Impression.—The diagnosis was that of possible abortive poliomyelitis.

CASE A-1.—A Wave, aged 21, whose roommate had been admitted with a diagnosis of poliomyelitis four days previously, was first seen on the night before her admission, complaining of headache. The generalized headache had begun on June

30, while the patient was working in the family clinic. It had persisted unabated. Except for a general feeling of tiredness, the patient had no other symptoms until the day before admission. On the morning of July 4 she began to notice aching in her neck and the upper part of her back. She had no fever. She was examined that night, when, except for slight stiffness and tenderness (and accentuation of headache) on bending of the neck, there were no positive findings. The reflexes were normal, and there was no evidence of muscular weakness or spasm. The next morning, July 5, the day of admission, the patient was unable to get out of bed. Her neck and the upper part of her back were stiff, and her headache was severe. She had no fever.

Physical Examination on Admission.—The temperature was 98.6 F., the respiratory rate 20 and the pulse rate 84. The patient, who was well developed and well nourished, appeared acutely ill. Physical examination revealed nothing of significance except severe stiffness and pain in the neck and back. The headache was intense. The reflexes were normal. There was no evidence of muscular weakness. The patient appeared somewhat generally weak. She could not sit up.

Spinal Fluid.—The cell count was zero; the total protein content, 15 mg. per hundred cubic centimeters.

Course in Hospital.—During the patient's first day in the hospital her neck and back grew stiffer and she became increasingly uncomfortable. Repeated examinations of the spinal fluid revealed a normal picture (2 lymphocytes per cubic millimeter and 10 mg. of protein per hundred cubic centimeters). That night her symptoms reached their peak; and from July 7 until her discharge, on July 12, there were gradual recession of the neck ache, backache and stiffness and gradual diminution of the headache. For three or four days, however, she had severe headache and neck ache on standing for more than a few minutes. Throughout her stay in the hospital her temperature remained normal, and she gave no evidence of muscular weakness at any time.

Impression.—The diagnosis was probable abortive poliomyelitis.

CASE A-8.—A boy aged 4½ years was admitted for observation on July 12, complaining of pain and stiffness in the left leg, which caused him to limp. About June 5 he had spent three days in bed with fever (temperature, 102 to 103 F.), sore throat and headache. About June 15 he began to feel dizzy and "dopey," and his legs were weak. These symptoms lasted two weeks. Three days after the initial symptoms the left leg and thigh began to hurt and to tire easily. From that time until his admission he complained of pain and stiffness in his left leg. On the day before admission a definite limp developed. He had no stiffness of the neck or back. There was no further fever. Examination revealed a normal status except for pronounced spasm of the hamstring muscles and around the hip on the left side. He improved rapidly under treatment with whirlpool baths and was allowed to go home after three days. No examination of the spinal fluid was made. He limped again at home for two days or so and then seemed well. He complained of occasional stiffness in the left thigh, but on subsequent weekly examinations no weakness was demonstrated.*

CASE A-9.—The mother of the boy in case A-8 also gave a history of a febrile episode at the time of her son's. She also had a slight limp about the same time that he did, but on the right side. She had had fever, headache and slight nuchal discomfort, but no definite stiffness or pain in the neck or back. She was examined by the physiatrist, who could demonstrate no definite weakness or spasm. After a few days her limp ceased.

Impression.—The diagnosis was possible abortive poliomyelitis.

CASE 8-A—A white woman aged 22, the mother of a patient with poliomyelitis, was admitted to the hospital on July 4, with the clinical diagnosis of poliomyelitis, made by her family physician. She complained of aching and stiffness of the neck and back, sore throat and weakness of the right arm and leg. She had been well until June 28, when her menstrual period began. During this monthly period and the preceding one there had been profuse menorrhagia. She had used at least twenty-four pads a day and was so weak that she stayed in bed most of the time. (Her periods were regular and usually lasted ten days.) While in bed, a week before her admission, and one week after her son was admitted with poliomyelitis, she noticed a low grade fever (temperature 99 to 100 F.), headache (chiefly occipital) and persistent drowsiness, hyperirritability, restlessness and malaise. Two days before her admission, a sore throat developed which continued until her entrance to the hospital; on the same day her right leg became weak (she noticed this when she walked across the room). The day before her admission her neck and back became increasingly stiff and ached. Her right arm and leg ached, and both became weak (the leg being the weaker). She vomited once and complained (in answer to questioning) of dysphagia and some regurgitation of fluids. Her headache was still present, and she said her temperature was 100 F. on the day before admission. On admission, she appeared rather weak, and was still menstruating.

Laboratory Data.—The spinal fluid was colorless, with no cells and a protein level of 10 mg. per hundred cubic centimeters. The white cell count was 9,200, with 58 per cent polymorphonuclear leukocytes (32 segmented and 26 nonsegmented forms), 36 per cent lymphocytes, 3 per cent eosinophils, 2 per cent basophils and 1 per cent monocyte. The red cell count was 3,900,000, with a hemoglobin concentration of 80 per cent. The urine was normal. The sedimentation rate was 8 mm. in one hour (Westergren method).

Physical Examination on Admission.—The temperature was 100 F., the pulse rate 80 and the respiratory rate 20, per minute. The blood pressure was 100 systolic and 70 diastolic. The patient had a washed-out appearance and seemed to be in considerable pain and discomfort. She held her neck and back stiff and complained of considerable tenderness on motion. There was apparent weakness of both the right arm and the right leg. The physiatrist noted muscular spasm in the right shoulder girdle and the right hip. All the reflexes were normal. The patient spoke in a very weak voice. She lay quite still.

Course in Hospital and Treatment.—After physical examination and studies of the spinal fluid, the patient was admitted to the hospital for observation. Two hours after her admission the physician on call was summoned because the patient began to have "muscle spasms" in her hands and arms and numbness and "drawing" of both hands. The patient exhibited a typical hyperventilation syndrome. There were bilateral carpal spasm and some laryngeal spasm, and the patient (as the hyperventilation increased) complained of severe dyspnea, dysphonia and dysphagia. Rapid intravenous administration of calcium gluconate stopped the hyperventilation. Then, sodium amytal, $7\frac{1}{2}$ grains (0.49 Gm.) was given slowly intravenously. The patient became clinically intoxicated; she then readily got up and walked about, without a trace of weakness or stiffness, and began joking with the physician. At no time after the amytal session did she exhibit any evidence of tenderness or stiffness in the neck, back or other muscles. She had no further complaints and returned home feeling quite well, after four days.

Impression.—The diagnosis was hysteria and possible mild abortive poliomyelitis.

COMPLICATIONS

Two children (1 in Jackson Memorial Hospital and the other in Key West) had complicating chickenpox. One of the pregnant women with a history of pyelitis had two further episodes of the infection, the last one being complicated with septicemia (*E. coli*). This condition responded to sulfadiazine.

Poliomyelitis had apparently no effect on any of the pregnancies.

TREATMENT

The treatment in general was that followed by the Georgia Warm Springs Foundation. Special instructions were given the nursing staff with respect to general nursing care; use of hot packs, baths and passive motion; reeducation of muscles, and prolonged observation and treatment after the acute stage of the disease.

SUMMARY AND CONCLUSIONS

1. The clinical and epidemiologic study of an epidemic of 40 verified cases of poliomyelitis and 190 cases of suspected and probable abortive poliomyelitis on the island of Key West is presented.

2. The largest number of pregnant patients (7) reported in any epidemic occurred here. Six had the paralytic form. The possible influence of the endocrine glands and the vitamins is noted.

3. An unusually high number (73.7 per cent) of patients in Navy families were adults (19 to 33 years of age), whereas only 10.5 per cent of the civilian patients were adults.

4. There were 3 instances in which 2 verified cases occurred in the same family (6 patients). Thirteen of the remaining 34 patients gave a history of a febrile illness resembling poliomyelitis in one or more of the family at the same time.

5. Eight patients had a normal temperature on admission. In an epidemic, this is a point worth emphasizing. Since fever is usually a cardinal sign of infection, a patient suspected of having poliomyelitis who has no fever, but mild symptoms, may be prematurely dismissed. It is important, then, to inquire routinely about recent fever or to watch for the subsequent development of fever.

6. In this epidemic a history of direct contact with persons known to have poliomyelitis was obtained for 18 (almost one half) of the patients. Polluted beach water and flies were also possibly incriminated in the transmission of the virus. Three children, said by their parents to have been completely isolated since the onset of the epidemic, had the disease. One patient was visited by the mother of a patient with acute poliomyelitis seventeen days prior to development of symptoms.

Abstracts from Current Literature.

Physiology and Biochemistry

SOME NEUROLOGICAL SIGNS AND SYMPTOMS PRODUCED BY CENTRIFUGAL FORCE IN MAN. W. R. FRANKS, W. K. KERR and B. ROSE, *J. Physiol.* **104**:10P, 1945.

The authors made an extensive study of the neurologic effects of centrifugal force in man on 532 subjects in the human centrifuge with forces varying from 2 to 10 G. The reaction times for manual responses to visual and auditory stimuli were recorded, but were not significantly increased except for visual stimuli immediately before black-out. Convulsions frequently occurred, usually after loss of consciousness. These were usually slight, but in a few cases severe generalized convulsions were observed. A number of slight convulsions were noted in fully conscious subjects. Conjugate movements of the head and eyes to one side were sometimes observed. Dreams were frequently experienced. Paresthesias, confused state, amnesia or gustatory sensations were noted with black-out. Incontinence was never observed. Convulsions started during the phase of recovery of the circulatory changes but could not be correlated with any of the measured characteristics of the subjects. Electroencephalograms during increased G in conscious subjects showed high frequency, low amplitude waves replacing the normal alpha waves. With onset of unconsciousness progressively slower waves of high amplitude usually appeared. The pattern was not altered by convulsions. THOMAS, Philadelphia.

THE EFFECT OF DIET ON FOETAL DEVELOPMENT. L. R. WALLACE, *J. Physiol.* **104**:34P, 1946.

An investigation was conducted to decide the effect of maternal diet on the various component parts of the fetus. By feeding ewes on a much restricted ration during the last eight weeks of pregnancy, 144 day old fetuses were obtained whose mean weight averaged only 57 per cent of that of fetuses obtained from liberally fed ewes. Fetuses were also obtained at the ninety-first day of pregnancy, when the experimental treatments commenced. The data resulting from the dissection of these groups of fetuses were compared with the data for fetuses from well fed ewes at twenty-eight day intervals from service.

The results showed that under conditions of restricted nutrition nerve tissue competed for available nutrients more effectively than bone, and bone more effectively than flesh (muscle and fat). Growth of nerve tissue and bone was not depressed as much as that of the fetus as a whole, but growth of flesh more so. The alimentary tract was less affected than the heart; the heart, less than the lungs and kidneys, and the latter, in turn, less than the thymus, spleen and liver.

Wallace concludes that the manner in which the weight increment made by the fetus during any particular period is distributed among the component parts of the body will depend on the extent to which the nutritive conditions then prevailing are limiting the rate of growth of the fetus.

THOMAS, Philadelphia.

EXPERIMENTS ON THE HYPOTHALAMIC-PITUITARY CONTROL OF WATER EXCRETION IN DOGS. MARY PICKFORD and A. E. RITCHIE, *J. Physiol.* **104**:105, 1945.

The daily urinary excretion of water and the immediate diuretic response to the administration of water and isotonic solution of sodium chloride (0.9 per cent) were

observed in dogs before and after the following operations: (a) removal of the posterior lobe of the hypophysis alone; (b) section of the supraoptic tracts; (c) attempted removal of the anterior lobe alone; (d) simple hypophysectomy, i. e., removal of the posterior and the anterior lobe at the same time and some of the stalk; (e) simple hypophysectomy and section of the supraoptic tracts at the same time.

After any operation involving loss of the anterior lobe the diuretic response to water was diminished as compared with the normal. The creatinine and urea clearances also fell. The diuretic response to the administration of isotonic solution of sodium chloride tended to be greater than the response to the administration of water. The blood pressure remained normal. Denervation of the kidneys did not affect the appearance of the changes mentioned. Dried thyroid, extracts of the anterior lobe of the pituitary gland and of the adrenal cortex and desoxycorticosterone acetate were not found to restore the diminished water diuresis or the lowered renal clearances to normal.

After section of the supraoptic tracts or removal of the posterior lobe alone water diuresis was normal or increased. The average creatinine clearances lay in the normal range. The diuretic response to the administration of isotonic solution of sodium chloride was greater than before operation.

Polyuria may follow any of these operations, even in the absence of the anterior lobe, but only after section of the supraoptic tracts was it of fairly long duration.

THOMAS, Philadelphia.

Diseases of the Brain

NEUROLOGICAL EXPERIENCES IN THE MIDDLE EAST AND INDIA. DOUGLAS McALPINE, *Proc. Roy. Soc. Med.* **39**:169 (Feb.) 1946.

Infections of the central and peripheral nervous systems were the main concern of the neurologist in the British armed forces in the Middle East and India. Meningococcic meningitis, practically confined to Indian and African troops, was laid to overcrowding and malnutrition during the winter months. The decrease in mortality from 15 per cent, in early 1943, to 6.6 per cent, in early 1945, and an even greater drop in the incidence of the disease, resulted, according to McAlpine, from the earlier diagnosis and hospitalization, a better standard of medical care and the use of "sulfamezathine" (the dimethyl derivative of sulfadiazine).

Acute benign lymphocytic meningitis occurred in the spring and summer months and was characterized by malaise, fever (averaging five days in duration), headache, vomiting and a considerable degree of prostration. There was variable nuchal rigidity; Kernig's sign was not usually elicited, and the deep reflexes were normal or depressed. The cell count of the cerebrospinal fluid was 20 to several hundred lymphocytes per cubic millimeter predominating, with a return to normal within three weeks.

Tick-borne relapsing fever was frequently complicated by infection of the nervous system. Of 84 cases with neurologic signs, the author observed meningitis in 95 per cent, with the cerebrospinal fluid characterized by pleocytosis, increased protein, often a positive Wassermann reaction and/or a gold curve characteristic of dementia paralytica. Meningoencephalitis was found in 28 per cent; facial palsy, in 21 per cent (bilateral in 4 cases), and papilledema, in 13 per cent. The prognosis with regard to neurologic sequelae was favorable. Arsenical treatment gave disappointing results.

Acute poliomyelitis was described as being commoner than in the British Isles but was rare among the Indian troops. The mortality rate ranged from 18 to over 30 per cent. Prodromal symptoms were roughly divisible into influenzal, catarrhal and gastrointestinal forms. The commonest site of localization was the lower dorsal and lumbosacral portions of the cord. Approximately 50 per cent of the patients had varying degrees of urinary retention. Fatal cases were of the ascending, cervicobulbar or bulbar type. Persistent pain in the paralyzed limb was a frequent occurrence. In approximately 5 per cent of the cases the cerebrospinal fluid was normal during either the meningitic or the paralytic phase.

Polyneuritis, either diphtheritic (exceedingly rare among native troops) or nutritional, was frequently observed. The diphtheritic form, commoner in the Middle East, was considered a complication of the cutaneous form of the disease in about one third of the cases. Nutritional polyneuritis complicated typhoid and, to a greater degree, typhus.

One of the principal medical causes of death in India was heat stroke, with several survivors showing permanent sequelae. After recovery from coma, progressive improvement occurred except in a small percentage of cases, in which some signs of dementia remained. Among neurologic sequelae, cerebellar signs were found in several patients.

BERRY, Philadelphia.

OBSCURE NEUROPATHY IN THE MIDDLE EAST: REPORT ON ONE HUNDRED AND TWELVE CASES IN PRISONERS-OF-WAR. J. D. SPILLANE and G. I. SCOTT, *Lancet* 2:261 (Sept. 1) 1945.

Spillane and Scott report their observations on a neurologic syndrome which they noted among German prisoners of war. The syndrome, of which they found 112 cases, consisted of retrobulbar neuritis, nerve deafness and ataxic paraplegia, but in many cases only the visual manifestations developed. The illness usually began with failing vision. In some cases this was acute, but in the majority it developed over a period of months. Tinnitus and gradual onset of bilateral deafness frequently accompanied the loss of vision, but in several cases they appeared weeks or months later. Paresthesias of the lower limbs constituted another characteristic complaint in many cases, and in some instances it heralded the onset of disturbances of gait and station. In some cases gross attacks of ataxic paraplegia occurred. There were other occasional neurologic signs, such as trigeminal hypesthesia, loss of taste and smell and partial paresis of the vocal cords. The illness was afebrile, chronic and, in many cases, progressive.

The syndrome was observed almost entirely in a particular camp, the inmates of which had previously been exposed to dietetic deprivations and in which pellagra, dysentery and diarrhea had at one time been prevalent. The authors state the belief that the patients were suffering from a nutritional neuropathy. They are unable to explain why the central nervous system was mainly attacked, in the absence of the common manifestations of nutritional deficiency among the patients affected. Patients who were given intensive treatment with the vitamin B complex responded poorly, or not at all. The results of dietetic therapy were also inconclusive.

YASKIN, Camden, N. J.

SUDDEN APPEARANCE OF PARKINSONIAN SYNDROME AFTER BURIAL UNDER BOMBARDMENT RUINS. M. D. DÉNÉCHAU, *Rev. neurol.* 77:80 (March-April) 1945.

Dénéchau reports the sudden appearance of parkinsonism in a man of 33 after burial under ruins during a bombing. The patient had had encephalitis lethargica twenty years previously. He was admitted to the hospital on Oct. 16, 1944 for

tremor of the left upper extremity and difficulty in memory and thinking. He had been active and apparently normal up to June 7, 1944, when he was buried under the ruins of a house during the course of a bombing attack. There was no loss of consciousness or serious injury to any part of the body. When removed from the ruins, he had generalized tremulousness and inability to walk to a hotel 200 meters away without being supported. He remained in this state about fifteen days. The generalized tremulousness then gradually disappeared, and tremor of the left upper extremity was noted. The patient found it difficult to work; he exhibited some sexual erethism and change in character and suffered from headache and somnolence. Neurologic examination showed typical parkinsonism, with fixed facies and loss of associated movements; a cogwheel phenomenon was present in the left upper limb. There was a history of cranial trauma at the age of 2 years and of severe chorea at the age of 7. Careful anamnestic studies revealed that for a few months before the bombing incident the patient had been aware of awkwardness of the left upper extremity. The author apparently believes that the accident transformed a latent or subclinical parkinsonism into the full blown form.

N. SAVITSKY, New York.

TRAUMA AND NEUROSYPHILIS. J. M. TAQUES BITTENCOURT and H. M. CANELAS, *Arq. neuro-psiquiat. São Paulo* 3:347 (Dec.) 1945.

In addition to an exhaustive review of the literature on the relation of trauma and neurosyphilis, Taques Bittencourt and Canelas report their experiences with 13 personally observed cases—3 of vascular and 10 of parenchymatous neurosyphilis. They conclude that trauma may aggravate preexisting neurosyphilis, precipitate latent or asymptomatic neurosyphilis and be a cause of localization of syphilis in the nervous system even when it is not involved prior to the trauma. They report for the first time 2 cases in which the spinal fluid gave negative reactions immediately after trauma and positive reactions later. The authors conclude that when the intercalary period between the trauma and the onset of the neurosyphilis is between one and six months a causal relation to the trauma is probable; when the interval is six to thirty months the relation to the trauma is more probable, and when the interval is longer than thirty months the relation to the trauma is least probable. While the presence of bridging symptoms between the time of the trauma and the onset of the neurosyphilis is desirable for the establishment of a causal relation, it is not a *sine qua non*. The authors conclude that trauma causes neurosyphilis as a result of significant alterations in the hematoencephalic barrier without gross vascular lesions by altering tissue immunity in the nervous system and by creating tissue changes which are favorable to the growth of spirochetes.

N. SAVITSKY, New York.

VENEZUELAN EQUINE MENINGOENCEPHALITIS IN MAN. H. R. RUGIERO, A. S. PARODI and A. C. SAENZ, *Prensa med. argent.* 33:636 (March 22) 1946.

The authors report 8 cases of equine meningoencephalitis in man, all the patients being infected in the same laboratory. Four cases were studied only clinically. In 2 cases the presence of the virus was proved serologically. The serum of patients in convalescence was mixed with the virus and then injected intraperitoneally into rats. In 2 cases the virus was demonstrated directly. In 1 case the clinical picture was very severe, with paralysis of all the limbs, somnolence, violent headaches, fever and delirium. In another case there were two bouts of hyperpyrexia, separated by an afebrile period of two days. The clinical picture in the other cases was that of grip, of greater or less severity—severe headache, diffuse aching, intense myalgia

and backache. Cutaneous hyperesthesia was present in 1 case. There was nothing about the clinical picture to distinguish it from that of other virus infections. The intensity of antibody formation bore no relation to the severity of the acute infection.

N. SAVITSKY, New York.

DEMENTIA OF THALAMIC ORIGIN. E. GRÜNTAL, *Monatschr. f. Psychiat. u. Neurol.* **106**:114. 1942.

Grünthal reports a case in which progressive mental deterioration was associated with disease of the thalamus. The patient, a woman, had always been mentally deficient. She was married and had 3 children, who were said to be feeble-minded. However, she had been well adjusted until the age of 35, when gradual mental changes were noted. She began to have difficulty in managing her household affairs. At times she squandered money, and at other times she was excessively penurious. She became noisy, quarrelsome and forgetful and displayed erotic tendencies. These symptoms grew more pronounced, and she was hospitalized at the age of 41. At the hospital she had episodes of aggressive, noisy and fearful behavior, alternating with periods of underactivity and euphoria. She was often confused at night. She misidentified people and had auditory hallucinations. She presented labile emotional reactions, particularly childish laughter, which quickly changed to outbursts of rage. Serologic examination of the blood and the spinal fluid gave negative reactions. The patient's memory became defective, and there was gradually increasing mental deterioration. Fourteen years after her admission she was described as severely demented, out of contact and extremely apathetic. Three years later constant choreic movements developed bilaterally. Death occurred at the age of 60, with signs of bronchopneumonia.

Anatomic examination revealed that the cerebral cortex and white matter were normal, although the brain was small. The thalamus and the red nucleus showed severe alterations, which were bilateral and symmetric. In the thalamus, the changes were confined to the nucleus medialis dorsalis, the nucleus lateralis anterior and the anterior portion of the nucleus lateralis principalis. Most of the nerve cells had disappeared from these areas, and there was a pronounced increase in neuroglia, with perivascular accentuation of the process. The red nucleus was completely replaced with a glial scar. In the right corpus Luysi (nucleus hypothalamicus) one perivascular devastated area was observed. The white matter of the inferior olives showed a moderate increase of neuroglia. The changes were chronic and of long standing; they were apparently based on vascular disease, the nature of which could not be determined. The involvement of the red nucleus was considered responsible for the choreic disturbances. According to Grünthal, the point of greatest interest was that progressive mental decay of a type ordinarily associated with diffuse damage to the cerebral cortex must be attributed in this case to circumscribed thalamic lesions. He speculates that the loss of parts of the thalamus which are closely connected with the frontal lobe can produce mental symptoms similar to those produced by involvement of the frontal lobe itself.

ROTHSCHILD, Worcester, Mass.

Diseases of the Spinal Cord

CHRONIC PAIN AS RESIDUAL OF POLIOMYELITIS. J. M. NIELSEN, *Bull. Los Angeles Neurol. Soc.* **10**:85 (Sept.-Dec.) 1945.

Nielsen observed a new syndrome of chronic pain as a residual of polyneuritic poliomyelitis in 15 cases in southern California. Reports of 6 cases are presented. The condition is characterized by neuritic and radicular pains, acroparesthesias

and a myotonic syndrome resembling myotonia congenita. After a subacute onset of pain, the course becomes chronic and continues for years, with exacerbations and remissions, possibly with a slow downward course. The sharp, shooting pains are almost exactly like those of *tabes dorsalis*. They affect not only the extremities but also the roots of the trunk and those supplying the trigeminal area. The pains differ from those of *tabes* in that they do not leave areas of hyperesthesia unless they become almost constant, and then late in the disease. Large areas are extremely sensitive to light touch but not to heavy pressure. All symptoms of destruction are extremely rare; the syndrome is almost exclusively irritative. The distribution of the gripping pains is that of the peripheral nerves. The acroparesthesia, the typical numbness of the hands and feet, is exactly like that of any sensory polyneuritis. The muscle spasms and myotonic syndrome do not seem related to any circulatory deficiency but, rather, appear to concern the muscles themselves or their nerve supply. But the anomalous condition exists that there is no tenderness of the nerve trunks or of the muscles in which the supposedly affected nerve endings are located unless the muscles are forced to contract many times by voluntary use. After such exercise there are much spontaneous pain in the group and a burning pain referred to the overlying skin. So far as is known, the syndrome does not respond to any treatment.

J. A. M. A.

DAMAGED INTERVERTEBRAL DISK: EARLY DIAGNOSIS AND TREATMENT. E. J. CRISP, *Lancet* 2:422 (Oct. 6) 1945.

The lumbar intervertebral disks suffer trauma far oftener than is generally appreciated, but in the absence of crural pain or roentgenographic changes the resulting lesion is often mistaken for sacroilac strain or fibrositis. Crisp states that in the early diagnosis of injured intervertebral disk the most significant objective sign is the intense spasm of the lumbar muscles and the "tight" lumbar portion of the spine. Patients with a lesion of this type often suffer recurrent attacks of acute lumbago, indicative of further trauma, and the true nature of the condition may be recognized only when the disk ruptures completely.

Early diagnosis and treatment with immobilization will considerably reduce the incidence of sciatica. The author divides cases which escape diagnosis until after the onset of sciatic pain into two groups, depending on whether the annulus fibrosus is partially or completely ruptured. The first group may be recognized by a fixed lumbar lordosis; the second, by a fixed lumbar kyphosis. In both groups the lesion usually responds well to immobilization in a plaster spinal jacket. Surgical treatment may be reserved for cases in which the protrusion has not been reduced after a period of immobilization of three months, for cases of recurrent protrusion, and for cases in which severe pain persists long after the lumbar portion of the spine has reverted to its normal curve.

YASKIN, Camden, N. J.

PROTRUSION OF INTERVERTEBRAL DISK. B. H. BURNS and R. H. YOUNG, *Lancet* 2:424 (Oct. 6) 1945.

Burns and Young conclude from their studies that recurrent backache in young adults is oftenest due to protrusion of an intervertebral disk. The earliest manifestation is backache, not sciatica. They regard what they call the orthopedic signs as being of the greatest importance in diagnosis of this condition. Not only is it possible to diagnose protrusion of the disk by the orthopedic signs alone, but in the early stages these are usually the only signs to be found. In many instances neurologic signs may make their appearance months, or occasionally years, after the onset of symptoms. The authors conclude that almost the only cause of sciatic scoliosis is protrusion of a disk. The most notable and constant characteristic of

protrusion of a disk is restriction of movement in the anteroposterior plane, whereas bending sidewise is free. The straight leg-raising test (Lasègue's sign) is of limited value. When the symptoms are slight and have never been severe, the authors recommend the patient to wear a belt or corset to restrict the movement of the lumbar portion of the spine. They do not favor the use of a plastic jacket, for it has proved a less comfortable, and no more effective, means of immobilization than a corset. Application of heat, massage, electrotherapy and injections of procaine may give temporary benefit in an attack by relieving spasm, but their effect, if any, is only transitory. The authors use a free exposure in operation because it gives easier access and a more comprehensive view of the lesion than the small interligamentous approach of a hemilaminectomy. The fifth lumbar and adjacent parts of the fourth lumbar and first sacral spinous processes are removed. The dura is then exposed by removing the lamina of the fifth lumbar vertebra and the adjacent ligamentum subflavum. The dura is not opened, and care is taken to avoid damage to the lateral vertebral joints. The authors conclude that precise localization can be achieved only by laminectomy. Myelographic studies and neurologic signs are of no help in localization. The use of contrast mediums and pneumograms has been abandoned.

Of 177 cases in which laminectomies were performed for suspected lesions of the disk, protrusions were found in 141. In 19 of the other cases intraspinal abnormalities capable of producing the symptoms were found. Of the 141 cases with proved lesions of the disk, immediate relief was obtained in 131, and the patients have remained free of symptoms.

YASKIN, Camden, N. J.

LUMBAGO: MECHANISM OF DURAL PAIN. J. CYRIAX, *Lancet* 2:427 (Oct. 6) 1945.

Lumbago is defined as lumbar pain of sudden onset, severe enough to immobilize the patient for a short time. The pain is usually equal on the two sides of the back; occasionally it is asymmetric; strictly unilateral pain is uncommon. It is the author's opinion that the result of such an attack of pain is an internal derangement of a low lumbar intervertebral joint, as the result of a momentary posterior displacement of a movable piece of intra-articular fibrocartilage. The prolonged subsequent pain appears to be caused entirely by bruising of the dura mater. Lumbago provides the stage of symptoms due to a hypermobile or fragmented annulus fibrosus that is intermediate in degree between backache and sciatica. Defect of the fibrocartilaginous ring leading to pressure exerted on the dura mater via the posterior capsular ligaments is a common, but hitherto unrecognized, cause of backache. The best treatment for this condition appears to be a few days' rest in bed, followed, if symptoms persist, by epidural local anesthesia. The technic of anesthetization is as follows: The patient lies prone, and the cornua of the sacrum are identified. The skin between them is anesthetized with not more than 1 cc. of a 0.2 per cent solution of procaine hydrochloride. Too much solution introduced here obscures the landmarks. A lumbar puncture needle is inserted into the sacral hiatus and passed to a depth of 3 inches (7.5 cm.). The stylet is withdrawn and care taken to see that neither blood nor cerebrospinal fluid escapes. A 50 cc. syringe full of 0.5 per cent procaine hydrochloride in isotonic solution of sodium chloride is attached to the needle. The contents are slowly injected over a period of five to ten minutes.

Prophylaxis after recovery from an attack of lumbago consists in the maintenance of the lumbar lordosis. Radical cure, i. e., removal of the hypermobile or loose part of the annulus, presents such technical difficulties that the author has not recommended it until the stage of sciatica from root pressure has been reached.

YASKIN, Camden, N. J.

FAMILIAL POLIOMYELITIS: REPORT OF CASES. RAUL MAGGI, Rev. Asoc. méd. argent. **59:302** (April 15) 1945.

Thirty-six of 600 cases (6 per cent) of poliomyelitis observed during the epidemic of 1942-1943 were familial, more than 1 case occurring in 17 families. In 15 families there were 2 cases each; in 2 families there were 3 cases each. In 8 instances the second case appeared simultaneously with the first; in 9 cases the second case came on from the third to the seventeenth day after the initial case in the family. In 2 cases no data were available on the interval between the primary and the secondary cases. Twenty-eight cases were of the paralytic and 8 of the nonparalytic form. Paralytic phenomena were more frequent in the initial cases.

N. SAVITSKY, New York.

ACUTE ANTERIOR POLIOMYELITIS COMPLICATING PREGNANCY. E. WAALER, Acta med. Scandinav. **123:209**, 1946.

Waal reports 8 cases of poliomyelitis in pregnant women between 18 and 38 years of age. Seven cases occurred during an epidemic in Bergen, Norway, in 1941; the eighth case occurred in 1944. There were 2 fatalities. The author observed that poliomyelitis is no severer in pregnant women except during the last months of pregnancy, when there may be great discomfort if the respiratory muscles are involved. The prognosis is probably worse for the mother in late than in early pregnancy. The disease has little influence on pregnancy and labor. Labor is usually normal, and cesarean section is indicated only when paralysis embarrasses the respiration or when genitourinary complications are serious. It is likely that poliomyelitis is more frequent in pregnant women than in other adults, and the cases hitherto observed have been uniformly distributed with respect to the various stages of pregnancy. No evidence has been produced of intrauterine transmission of poliomyelitis. In this series of cases, the 5 live-born infants did not show any sign of paralysis or malformation. Follow-up investigation at the age of 3 years showed that all the children were well and that they had learned to walk at the usual age. In 1 case of stillbirth with spontaneous labor there was a history of previous stillbirth and no evidence that poliomyelitis was responsible. Microscopic examination of the nervous system of the fetuses of the 2 mothers who died in the sixth and the eighth month, of pregnancy, respectively, did not reveal any abnormality.

J. A. M. A.

Treatment, Neurosurgery

MODIFICATION OF THE ELECTRO-SHOCK CONVULSION BY SODIUM PENTOTHAL AND CURARE. MATTHEW BRODY, J. Nerv. & Ment. Dis. **102:357** (Oct.) 1945.

While intravenous injection of sodium pentothal produces excellent narcosis, its relaxing effect is poor. The usefulness of the drug in conjunction with electroshock therapy is, therefore, limited, although it may be employed to produce a modified type of convulsion. Curare and sodium pentothal used together produce both narcosis and relaxation, thus reducing the risk of injury and obliterating the postconvulsive excitement in apprehensive, uncooperative or disturbed patients. Three hundred milligrams of freshly prepared sodium pentothal in 2.5 per cent solution is injected intravenously over a period of thirty seconds. With the same needle, but a different syringe, 0.45 mg. of curare ("intocostin") per pound (0.5 Kg.) of body weight is injected slowly, over a period of a minute. The electrodes are applied, and four minutes after the injection is begun the current is applied.

Higher voltages or longer applications of current may be required. With this method, it is possible to treat extramurally patients who would otherwise require institutionalization.

CHODOFF, Washington, D. C.

INTRATHECAL AND ORAL VITAMIN THERAPY IN VARIOUS NEUROLOGIC DISORDERS.

G. HEILBRUNN and N. HOFFENBERG, *J. Nerv. & Ment. Dis.* **102**:379 (Oct.) 1945.

Heilbrunn and Hoffenberg treated 15 patients with various disorders of the nervous system by the use of daily oral administration of 75 mg. of "ephynal acetate" (alpha tocopherol acetate), 6 mg. of thiamine hydrochloride, 3 mg. of riboflavin, 1.5 mg. of pyridoxine hydrochloride, 30 mg. of nicotinamide and 3 mg. of calcium pantothenate and weekly spinal injections of increasing doses (25 to 100 mg.) of crystalline thiamine hydrochloride. The treatment was continued for an average of nine and a half weeks. Of the 15 patients, 2, with a disorder diagnosed as tabes dorsalis, showed definite improvement, both subjectively and objectively. The other patients, with diseases which included Huntington's chorea, multiple sclerosis, lateral sclerosis; disseminated encephalomyelitis and postencephalitic parkinsonism, failed to show any favorable change. The authors believe that the improvement in the cases of tabes is probably significant and suggest that the lesions responsible for the condition may be due to a synergistic action of the spirochete and a latent nutritional deficiency.

CHODOFF, Washington, D. C.

ENDOLUMBAR PNEUMOENCEPHALOGRAPHY, SIMPLIFIED. JOSEPH H. GLOBUS and JOHN L. SIMON, *J. Nerv. & Ment. Dis.* **102**:412 (Oct.) 1945.

In order to make the procedure of pneumoencephalography less painful and shocking to the patient, the authors have devised a method by which the patient is kept lying on his side in bed, instead of being fastened in a chair in a sitting position. To obtain the necessary elevation of the patient's head to insure a rapid rise of the introduced air, the head of the bed is raised by placing the legs on tall shock blocks or on two chairs. This method has been employed in 28 cases, with satisfactory visualization in 22 cases, and without discomfort to the patient.

CHODOFF, Washington, D. C.

STREPTOMYCIN IN TUBERCULOUS MENINGITIS. R. E. COOKE, D. L. DUNPHY and F. G. BLAKE, *Yale J. Biol. & Med.* **18**:221 (Jan.) 1946.

Cooke and his co-workers report that a girl aged 1 year with tuberculous meningitis gave a history of intimate exposure to tuberculosis. A pulmonary lesion and a positive tuberculin test were demonstrated. The cerebrospinal fluid showed characteristic chemical and cytologic changes. Smears showed many acid-fast bacilli. Inoculation of guinea pigs produced the typical disease in five weeks, and the organisms were present in the lesions. Treatment with streptomycin began on the eighth hospital day. It was administered intramuscularly in an amount of 10,000 units in 1 cc. of isotonic solution of sodium chloride every two hours for the first week; 20,000 units was then given every two hours for thirty days. Because of lack of the drug, treatment was interrupted almost seven days. When therapy was resumed, the dosage of 20,000 units every two hours was continued for an additional twenty-nine days. The total amount of streptomycin given by intramuscular administration was 15,049,000 units, over a period of sixty-eight days. The initial daily amount of streptomycin given intrathecally was 1,000 units. This was gradually increased to 100,000 units by the fifteenth day of therapy. Two

hundred thousand units in 5 cc. of isotonic solution of sodium chloride was given intraventricularly every other day, beginning on the nineteenth day of treatment. Since the supply of streptomycin was becoming low, the amount was decreased to 100,000 units. There was a lapse of nine days in intrathecal administration, but treatment was resumed with 200,000 units every other day over a period of twenty-nine days. The total amount of intrathecal streptomycin was 4,951,000 units. The infant thus received a total of 20,000,000 units by the combined routes. The progression of tuberculous meningitis was arrested during treatment with streptomycin. The symptoms have decreased further since cessation of treatment. There is evidence that intramuscular and intrathecal administration of streptomycin favorably influenced the course of tuberculous meningitis in this case. This report is the first detailed account of the administration of streptomycin by the intrathecal route.

J. A. M. A

PAINFUL PHANTOM LIMB TREATED BY HIGH CERVICAL CHORDOTOMY: REPORT OF 2 CASES. M. A. FALCONER and J. S. B. LINDSAY, *Brit. J. Surg.* **33**:301 (April) 1946.

Falconer and Lindsay report 2 cases of painful phantom in the upper limb of an army corporal, aged 27, and a war pensioner, aged 33, who were relieved by high cervical chordotomy performed by controlled graduated division, with local anesthesia. These 2 cases did not belong to the group in which relief was obtained by interruption of peripheral or sympathetic nerve pathways and in which pain impulses appear to arise in or around the neuromas of the divided nerves; they belonged to the other main group, in which painful impulses arise in the dorsal horn cells of the spinal cord and can be relieved only by section of the spinothalamic tract or by excision of the sensory cortex of the cerebrum. Infiltration of the appropriate peripheral or sympathetic pathways with a local anesthetic solution is a useful diagnostic procedure for distinguishing clinically between these two groups. When these diagnostic tests fail to give relief, section of the spinothalamic tract is suggested, and seems preferable to ablation of the sensory cortex because it does not destroy postural and other discriminative sensations in the stump, but only abstracts from it the sensation of pain and so renders the stump functionally useful for such purposes as carrying an artificial limb.

J. A. M. A.

PREFRONTAL LEUCOTOMY IN TREATMENT OF POST-ENCEPHALITIC CONDUCT DISORDER. F. T. THORPE, *Brit. M. J.* **1**:312 (March 2) 1946.

Thorpe describes 2 cases of adults aged 28 and 31, respectively, with post-encephalitic parkinsonism in which severe behavior disorders, present since childhood, were improved by means of bilateral prefrontal leukotomy. Complete amelioration of the aggressive and impulsive trends has been maintained in both cases for twenty-four and fourteen months, respectively.

In a study of 144 cases of severe disorders, Gibbs found that the fundamental cause of much of the abnormal behavior was "a state of tension or irritability of affect, driving [the patient] to periodic outbursts of impulsive conduct of characteristic simplicity, unpremeditated and unplanned." Surgical division of the fiber connections between the thalamus and the prefrontal area of the brain reduces this emotional tension.

ECHOLS, New Orleans.

TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS IN INFANTS BY OPENING THE LAMINA TERMINALIS. JEAN GUILLAUME and CHARLES RIBADEAU-DUMAS, *Rev. neurol.* 77:173 (July-Aug.) 1945.

The authors report their experiences with the construction of an opening in the lamina terminalis, or the anterior wall of the third ventricle, in treatment of obstructive hydrocephalus. They report successful operations on 3 infants, 11, 6 and 3 months of age, respectively. The operations were performed with the use of local anesthesia. Two or three days before the operation ventricular drainage was carried out by means of puncture through the anterior fontanel. Such drainage facilitates adaptation of the brain to the altered hydrodynamic situation following the opening of the lamina terminalis. The authors suggest making a small puncture at first to allow the spinal fluid to flow slowly out of the ventricle; the opening is later enlarged. During the operation the ventricles are filled with Ringer's solution to prevent sudden collapse of the cerebral hemispheres. The operation in all 3 cases was successful so far as the enlargement of the head was concerned; in 1 case the head became smaller, and in another the child, who was blind, was able to see again.

N. SAVITSKY, New York.

Encephalography, Ventriculography, Roentgenography

DIAGNOSTIC VALUE OF PNEUMOENCEPHALOGRAPHY IN CASES OF DEMENTIA PARALYTICA. JEAN DELAY, P. NEVEU and P. L. DESCLAUX, *Rev. neurol.* 77:179 (July-Aug.) 1945.

The authors analyze the value of pneumoencephalographic studies in 33 cases of dementia paralytica. One hundred to 220 cc. of spinal fluid was removed and replaced with air. Four types of roentgenograms were noted after insufflation of air. 1. In 15 cases the sulci were widened over the entire cortex; the ventricles were dilated; the frontal horns seemed somewhat rounded, and there was some loss of normal contour. Air was noted over the vertex in the region of the falx. 2. In 7 cases the ventricles were dilated, especially in the frontal region, but air was not noted over the cortex. The number of sulci which were dilated were few, especially in the frontal region. It is possible that this absence of air over the cortex was due to edema of the leptomeninges obliterating the spaces in that region. 3. In 2 cases there were disseminated spots of atrophy over the whole cortex. The lateral and third ventricles were not visualized; the cisterns at the base were not altered. 4. In 5 cases the ventricles were nearly normal. There were occasional slight widening of the frontal horns and slight filling of the sulci over the frontal lobes with air, indicating a moderate degree of atrophy in that region. The prognosis in the cases of type 1 was very poor; the patients did not recover. The prognosis was also poor in the cases of type 2. In some of these cases the disappearance of serous accumulations in the meninges was noted after malarial therapy. In cases of type 3 the results with therapy were also poor. In all 5 cases of type 4 the condition cleared up with treatment. No similar correlation was found in cases of juvenile dementia paralytica. The authors note a case of dementia paralytica with progressive hemiparesis and coma in which encephalographic studies showed a shift of the ventricular system; a subdural hematoma was observed at operation. The authors note that the frontal lobe was predominantly involved in all cases. They were unable to verify the observation of Hermann and Hernheiser (*Ztschr. f. d. ges. Neurol.-u. Psychiat.* 96:730, 1925) that in cases of dementia paralytica with hallucinations the maximal changes in the pneumoencephalogram were noted in the region of the temporal lobes.

N. SAVITSKY, New York.

Obituaries

RICHARD HENRY HUTCHINGS, M.D.

1869-1947

Dr. Hutchings is dead. A man who for a generation was one of New York state's distinguished psychiatric figures is no more. While his example and inspirations are diminished, something of him will long remain.

Dr. Hutchings was born in 1869 and brought up in Georgia. He came to New York city in his early twenties, graduated from Bellevue Hospital Medical College in 1891 and served his internship on Blackwell's Island. He entered the service of the New York State Hospital in 1892 and continued in that service until he retired, in 1939. During his period of service, lasting forty-seven years, he was superintendent of the St. Lawrence State Hospital from 1900 to 1919 and superintendent of the Utica State Hospital from 1919 until his retirement, in 1939. He enlisted in the army during World War I and finished his federal service with the rank of major.

Many honors came to him, among them the presidency of the American Psychiatric Association in 1938. He was the head of the Oneida County Medical Association and a director of the National Committee for Mental Hygiene, made a survey of the State of Georgia at the request of its governor and in 1940 was given the honorary degree of Doctor of Science by Colgate University. During his later years he was the dean of New York psychiatrists and highly respected by his professional brothers.

Known to most of his associates as a person of limited physical stamina and handicapped by failing vision, men marveled at the acuteness of his mind and at his literary leanings. Early he saw that Freud had made a real contribution, and he combated, in his gentle way, the skepticisms of his contemporaries, never going too fast or too far, but always forward. When many men of his age were withdrawing, he published his famous "A Psychiatric Word Book" (Utica, N. Y.: State Hospitals Press), which, in its many editions, has found a place on the desks of psychiatrists, psychologists, psychiatric social workers and psychiatric nurses. For years he edited the *Psychiatric Quarterly*, wrote its editorials and saw it through the press, and up to the day of his death it was ever on his mind.

What an example Dr. Hutchings was! To his family he was a devoted husband and father, to his students an honored chief as well

as a professional guide and to his associates a trusted support. He could also be a considerable antagonist. Mentally alert, a southern gentleman in demeanor, he was a student to the last, with a deep interest in fine literature and the ability to use his resonant voice to express himself with studied dignified language. No one ever heard him use an uncouth word.

All of this went on for years in spite of slowly diminishing physical vigor, continued failing vision and episodes of acute ill health. With these handicaps who else would have struggled so manfully?

Richard Henry Hutchings died at his home in Clinton, N.Y., on Oct. 28, 1947 at the age of 78.

FREDERICK W. PARSON, M.D.

News and Comment

ANNOUNCEMENT OF POSTGRADUATE COURSES FOR QUALIFIED PHYSICIANS AT UNIVERSITY OF CALIFORNIA MEDICAL CENTER (1948)

The Faculty of the University of California Medical School, under the sponsorship of University Extension (Medical Extension), University of California, announce a full time postgraduate course in psychiatry and neurology, of twelve weeks, to begin about the middle of September 1948.

All these courses are available to veterans under the provisions of the G. I. Bill of Rights on presentation of a letter of eligibility and entitlement. Completed programs and details will be mailed on request to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22.

Book Reviews

Psychiatric Research. Papers read at the Dedication of the Laboratory for Biochemical Research, McLean Hospital, Waverley, Mass. By Cecil K. Drinker, M.D.; Jordi Folch, M.D.; Stanley Cobb, M.D.; Herbert S. Gasser, M.D.; Wilder Penfield, M.D., and Edward A. Strecker, M.D. Price, \$2. Pp. 113. Cambridge, Mass.: Harvard University Press, 1947.

The six papers read at this dedication ceremony, held on May 17, 1946, are here fittingly recorded as the ninth number of the Harvard University Monographs in Medicine and Public Health. The review by Dr. Folch, the director of the new laboratory, entitled "Biochemical Problems Related to Psychiatry," is a masterful exposition of a series of anatomic, biochemical, metabolic and energy characteristics of the brain in a manner which leads directly to a host of problems capable of laboratory investigation. Dr. Penfield delivered an informative and provocative lecture on "Psychical Seizures," suggestive of the possibilities involved in the investigation of "brain biology." Dr. Cobb's lecture was in the form of a report on the work which had been done in the psychiatric wards of the Massachusetts General Hospital, dealing at some length with the investigations conducted there on the relation of neurocirculatory aesthenia and anxiety states. Drs. Drinker, Gasser and Strecker gave lectures on the history of McLean Hospital, the positivist's approach to psychiatric research and the "Psychobiology of Psychiatric Research," respectively.

Thus, the biochemical cerebral biologic, psychobiologic, psychosomatic and behavioristic viewpoints on psychiatric research were each represented in this symposium. Unfortunately, an exposition of what can be expected from the sociologic approach to research problems in psychiatry is missing.

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